Prediction of cardiac ventricular arrhythmias

by echocardiography in patients at risk

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Kristina Hermann Haugaa,
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List of Papers

1. Haugaa KH**,** Edvardsen T, Leren TP, Gran JM, Smiseth OA, Amlie JP. Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome**.** Eur Heart J 2009, 30 (3): 330-7.

2. Haugaa KH, Amlie JP, Berge KE, Leren TP, Smiseth OA, Edvardsen T. Transmural differences in myocardial contraction in long QT syndrome - mechanical consequences of ion channel dysfunction. Circulation, 2010;122 (14):1355-63.

3. Haugaa KH, Smedsrud MK, Steen T, Kongsgaard E, Loennechen JP, Skjaerpe T, Voigt JU, Willems R, Smith G, Smiseth OA, Amlie JP, Edvardsen T. Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction. A novel method for risk prediction of ventricular arrhythmia. J Am Coll Cardiol Img 2010; 3:247-56.

4. Sarvari SI, Haugaa KH, Anfinsen OG, Leren TP, Smiseth OA, Kongsgaard E, Amlie JP, Edvardsen T. Right Ventricular Mechanical Dispersion is Related to Malignant Arrhythmias – a Study of Patients With Arrhythmogenic Right Ventricular Cardiomyopathy and Subclinical Right Ventricular Dysfunction. (Submitted).

Abbreviations

LQTS	Long QT syndrome
QTc	Rate corrected QT interval
APD	Action potential duration
ARVC	Arrhythmogenic right ventricular cardiomyopathy
MI	Myocardial infarction
LV	Left ventricular
EF	Ejection fraction
ICD	Implantable cardioverter defibrillator
TDI	Tissue Doppler imaging
PEV	Post ejection velocity
RV	Right ventricular
ROC	Receiver operating characteristics

Introduction

Cardiac ventricular arrhythmia is still the most common cause of sudden cardiac death occurring in about 1:1000 inhabitants per year (1). In individuals below 40 years of age, inherited cardiac disease is the most frequent cause of ventricular arrhythmias, while coronary artery disease is most common in individuals above 40 years of age. In this thesis, patients with increased risk of ventricular arrhythmias and sudden cardiac death from both categories were included with the overall aim to evaluate the role of novel echocardiographic techniques in risk stratification of ventricular arrhythmias.

The long QT syndrome

The long QT syndrome (LQTS) is an inherited cardiac arrhythmic disease predisposing to life threatening ventricular arrhythmias and sudden cardiac death. Mutations in genes encoding for cardiac ion channels are leading to prolonged action potential duration and dispersion of action potential repolarization which are considered to be important mechanisms behind the arrhythmias in these patients (Figure 1). Risk stratification for ventricular arrhythmias in LQTS patients is currently based on history of syncope, genotype, gender and heart rate corrected QT interval (QTc) on ECG (2). Prolonged QTc reflects prolonged myocardial action potential duration (APD). Earlier invasive studies have indicated that APD is not homogeneously distributed throughout the myocardium neither in healthy humans nor in genetically altered myocardium (3-6). Inhomogeneous end of APD has been reported as dispersion of electrical repolarization (7). In LQTS patients, this dispersion of APD leads to a marked electrical dispersion of repolarization which is important in arrhythmogenesis and the development of Torsade de pointes ventricular arrhythmia (Figure 1)

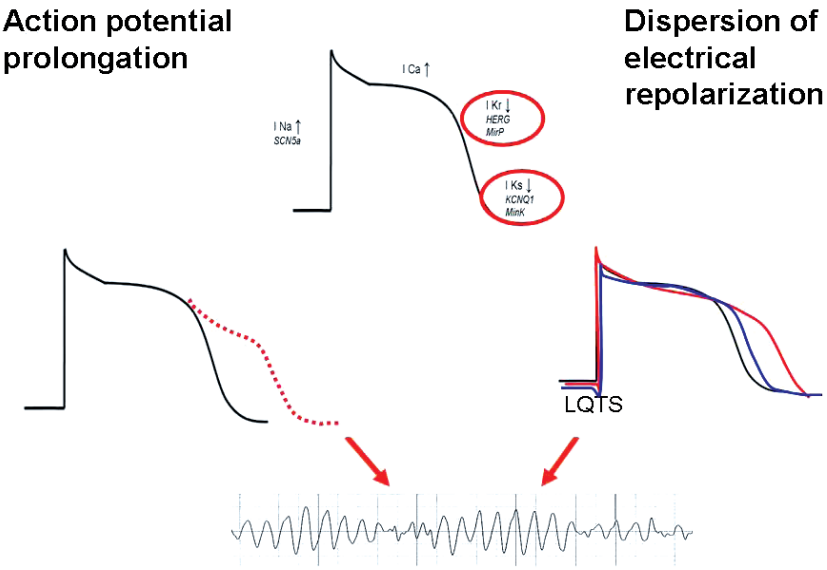

Figure 1. Mechanisms of arrhythmias in LQTS. Potassium channels (IKr and IKs, red circles) are the most frequently affected ion channels in LQTS. Defect ion channels lead to a prolongation of action potential duration (lower left panel). Action potential prolongation is inhomogeneously distributed throughout the ventricles leading to dispersion of electrical repolarization (lower right panel).

Dispersion of action potential repolarization can occur between apex and base i.e. longitudinally and transmurally (8, 9). Longest APD in LQTS models has been reported in endocardial Purkinje cells and in subendocardial to mid-myocardial cells (M-cells), while shortest APD occurs in epicardial cells (5, 10). These transmural APD duration differences have been defined as transmural electrical dispersion (4).

Life threatening ventricular arrhythmia occurring early in life is the gravest symptom of the LQTS. Genetic testing for LQTS has become more available and family screening has lead to a substantial amount of known individuals carrying an LQTS related mutation. However, the overall risk that adult asymptomatic mutation positive family members will experience arrhythmias during their lifetime is low and in these individuals QTc has failed to be a significant predictor

of outcome (11). Prophylactic treatment involves lifelong beta blocker therapy and decisions regarding preventive treatment is often challenging. Further risk stratification tools are needed.

Left ventricular (LV) function has been considered to be normal in LQTS patients and echocardiography in these patients has traditionally been performed only to exclude additional heart diseases. There is, however, support for the assumption that prolonged action potential duration and electrical dispersion may cause wall motion abnormalities in these patients which can be assessed by echocardiography (12, 13).

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inheritable, chronic and progressive cardiomyopathy and is one of the leading causes of sudden unexpected cardiac death in previously healthy young individuals (14, 15). Prevalence has been estimated to be at least 1 in 1000 (15).

Recent molecular genetic reports have revealed ARVC as mainly a desmosomal disease (16). Mutations in one of the 5 desmosomal or 3 extra desmosomal genes so far identified, lead to progressive loss of myocytes, followed by fibro-fatty replacement. Penetrance is age and gender dependent and the progressive clinical picture is highly variable (17).

Four clinical stages have been documented: An early concealed phase, overt electrical disorder, isolated right heart failure, and biventricular pump failure (15, 18, 19). Importantly, life-threatening arrhythmias can occur with only discrete or even absent myocardial structural changes (20). Risk stratification of ventricular arrhythmias and sudden cardiac death is therefore challenging.

Mechanisms for arrhythmias in early stages of ARVC are probably due to dysfunction of desmosomal proteins and disturbed cell to cell coupling (21). In later stages of ARVC when structural abnormalities in the myocardium have developed, reentrant ventricular arrhythmias can occur in tissue with fibro fatty replacement. Therefore, electrical conduction disturbances with consequent electrical dispersion has been suggested as an important mechanism of ventricular arrhythmias (22, 23).

Patients after myocardial infarction

Patients after myocardial infarction (MI) are at high risk for cardiac arrhythmic events and sudden cardiac death (1). Currently, LV ejection fraction (EF) is the primary parameter used to select patients for implantable cardioverter defibrillator (ICD) therapy after a MI. Impaired EF is shown to be a marker of increased cardiovascular mortality and sudden cardiac death. However, EF has relatively low sensitivity to detect arrhythmic risk (24). A number of other diagnostic tests have been proposed to improve the accuracy for selection of patients for ICD therapy. Currently available data, however, are not adequate to routinely recommend additional risk-stratification methods for selection of patients for ICD therapy (25).

The presence of myocardial scar forms the substrate for malignant arrhythmias (26). Heterogeneity in scar tissue may create areas of slow conduction that generate the substrate for ventricular arrhythmia post-myocardial infarction (27). Electrical dispersion, including both activation time and refractoriness, in infarcted tissue is a known arrhythmogenic factor (7, 28-30). Electrical abnormalities may lead to distorted myocardial function (31). Therefore, regional differences in electrical properties may cause heterogeneity of myocardial contraction which can be recognized as myocardial dyssynchrony (32).

Novel echocardiographic techniques; Tissue Doppler velocity and myocardial strain

Minor degrees of myocardial contraction heterogeneity and subtle contraction dyssynchrony can be demonstrated by modern echocardiographic techniques including tissue Doppler imaging and myocardial strain (33, 34). During a cardiac cycle, apex is relatively fixed, while basis is moving towards apex in systole. Myocardial tissue movement produces high amplitude Doppler signals, but has low velocity compared to blood flow. Tissue Doppler imaging (TDI) echocardiography has been introduced as a method to quantify longitudinal cardiac motion in terms of tissue velocities (35, 36). In Paper 1,

tissue Doppler velocities were mainly used to assess timing of myocardial contraction.

Myocardial strain is a measure of deformation of a defined cardiac segment. Strain is defined as the fractional change of tissue length and is expressed as percent shortening (or lengthening) of a segment during systole (34, 37). Strain by echocardiography has been demonstrated to be a more accurate tool for quantification of myocardial function compared to EF (38). Strain measurements were used in Paper 2-4.

In this thesis, tissue Doppler velocities and myocardial strain by echocardiography were used to accurately assess timing and function of myocardial contraction in patients with increased risk of ventricular arrhythmias. The hypotheses in this thesis were based on the assumption that arrhythmogenic electrical abnormalities will lead to mechanical alterations which can be assessed by TDI and strain echocardiography.

Aims of the thesis

General

To investigate if novel echocardiographic tools can improve risk stratification of life threatening ventricular arrhythmias in individuals at risk.

Specific

1. We aimed to investigate if LQTS patients with prolonged APD have prolonged myocardial contraction duration which can be assessed by TDI and strain echocardiography. Furthermore, if LQTS patients have contraction heterogeneity assessed as mechanical dispersion and if mechanical dispersion can be a marker of ventricular arrhythmias.
2. We aimed to investigate if there are regional contraction differences throughout the left ventricle in LQTS patients. We hypothesized that myocardial contraction is most prolonged in subendocardial myofibers in LQTS patients where longest APD has been reported. Furthermore, we aimed to investigate if inhomogeneous transmural contraction is related to risk of spontaneous arrhythmia.
3. We aimed to investigate if heterogeneity in infarcted myocardial tissue leads to contraction heterogeneity assessed as mechanical dispersion which can be assessed by myocardial strain echocardiography. Furthermore, if mechanical dispersion in patients after myocardial infarction can predict ventricular arrhythmias and if global strain by echocardiography is a better marker of arrhythmias than EF in these patients.
4. We aimed to investigate if ARVC patients have cardiac contraction heterogeneity assessed as mechanical dispersion which is associated with susceptibility to ventricular arrhythmias. Furthermore, if mechanical dispersion is present in ARVC mutation carriers in early stages of the disease where no structural alterations are visible.

Subjects

Patients with long QT syndrome

A total of 101 patients with molecularly defined LQTS were included in this thesis. Paper 1 included 73 of these LQTS patients. All patients were genotyped: 64 had LQT1 mutation (*KCNQ1*-gene), 26 LQT2 (*HERG*-gene), 1 LQT3 (*SCN5A*-gene), 1 LQT5 (*Mink*-gene) and 9 were double mutation carriers (*KCNQ1*-gene) and had clinically Jervell and Lange-Nielsen syndrome with concomitant deafness. In all, 48 (48%) had a history of documented arrhythmia, syncope or cardiac arrest, while 53 (52%) were asymptomatic mutation carriers recruited by family cascade genetic screening. We did not include asymptomatic mutation carriers younger than 18 years of age because we regarded them too young to be classified as true asymptomatic. None of the LQTS patients were ventricularly paced or had structural heart disease of other origin.

Patients with ICD after myocardial infarction

85 post-MI patients fulfilling indications for ICD therapy were recruited from 4 university hospitals (St.Olavs Hospital, Trondheim, Ullevål University Hospital, Oslo, University Hospital Gasthuisberg, Leuven, Belgium and Rikshospitalet University Hospital, Oslo). All patients were included prospectively with echocardiographic examination performed during the hospitalization for ICD implantation. Inclusion criteria were prior MI and indication for ICD therapy according to primary or secondary prevention criteria. Exclusion criteria were atrial fibrillation, left bundle branch block, previous coronary artery bypass graft surgery and valve regurgitations greater than moderate. Arrhythmic events during follow up were defined as ventricular arrhythmias that required appropriate anti tachycardia pacing (ATP) or shock from the ICD.

Patients with ARVC

Among 59 patients in the studygroup, 36 (61%) had symptomatic ARVC fulfilling 2010 International Task Force criteria (39), while 23 (39%) were asymptomatic mutation carriers, diagnosed by cascade genetic screening. ARVC related mutations were confirmed in 43 (73%) of all patients, (37 (86%) *PKP2*, 5 (12%) *DSP* and 1 (2%) *RYR2)*. Ventricular arrhythmias (sustained VT or VF) were documented in all 36 ARVC patients and 33 (92%) of these were treated with ICD in addition to medical antiarrhythmic therapy.

Control groups

Healthy individuals

A total of 58 healthy individuals were recruited from the hospital staff in order to correspond with age and sex of the patient groups. All had normal ECG and echocardiography and used no medication. In Paper 1, 20 healthy controls participated, in Paper 2, 35, 23 participated in Paper 3 and 30 in Paper 4.

Individuals on beta-blocker therapy

Since a substantial proportion of the LQTS patient group received beta blocker medication at inclusion time, 18 otherwise healthy individuals on beta-blocker therapy were included for comparison in Paper 1. They were treated with beta-blockers for suspected angina pectoris from the referral institution ahead of an elective coronary angiography. They all showed a normal clinical examination, coronary angiography, ECG, QTc and echocardiography.

Patients with prior MI without ventricular arrhythmias

From the outpatient clinic at Oslo University Hospital, Rikshospitalet we recruited 20 patients with prior MI for participation in Paper 3. None of these had arrhythmic events. Exclusion criteria were identical to the population with ICD after MI.

Methods

ECG

Twelve lead ECG was obtained at the time for echocardiographic examination. Bazett's formula was used for heart rate correction of the QT interval (40). QTc dispersion was measured as the difference between longest and shortest QTc interval in any of the 12 ECG leads (41).

Echocardiographic studies

The echocardiographic studies were performed using Vivid 7 (GE Healthcare, Horten, Norway) and analyzed with software EchoPAC®, GE. By conventional 2 dimensional echocardiography, we assessed LV EF ad modum Simpson. All echocardiographic time measurements were corrected for heart rate using Bazett's formula (40).

Tissue Doppler imaging

In Paper 1, two dimensional TDI recordings of the LV were obtained from apical 4 chamber, 2 chamber and long axis views as previously described (37). Three cycles were analyzed and mean image frame rate obtained in these studies was 124±29 frames/s.

Myocardial velocity parameters:

From myocardial velocity curves, following parameters were assessed:

1. Peak ejection velocity (Figure 2).

2. Peak myocardial velocity after aortic valve closure = post ejection velocity (PEV) (Figure 2).

3. Maximum PEV in absolute value, negative or positive, was measured and the anatomical location was noted in each participant.

4. Myocardial contraction duration was defined as the time from start of R on ECG to end of PEV (zero-crossing) if positive PEV was present.

If no positive PEV was present, contraction duration was defined as the time from start of R on ECG to zero-crossing of the decreasing velocity slope in end-systole (Figure 2).

5. Contraction duration of the basal segment of the six LV wall positions was measured and the standard deviation of these values calculated as a parameter of mechanical dispersion of contraction (Figure 3).

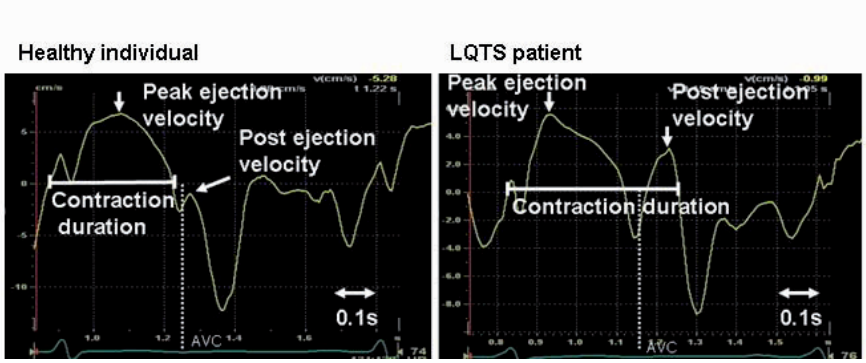

Figure 2. Myocardial contraction duration by tissue Doppler imaging. Myocardial velocities from a healthy individual (left panel) and an LQTS patient (right panel). Contraction duration was defined as time from start of R on ECG to end of post ejection velocity (zero-crossing). (Eur Heart J. 2009).

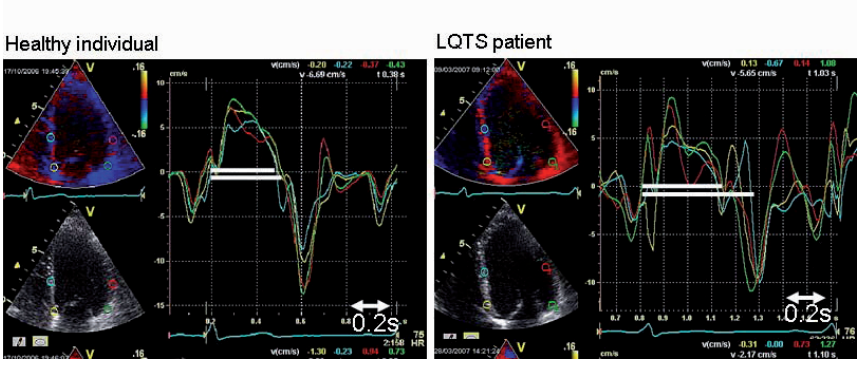

Figure 3. Myocardial mechanical dispersion by tissue Doppler imaging. The left panel shows velocity curves from four different segments in a healthy individual in 4-chamber view. The right panel shows velocity curves from a symptomatic LQTS patient. White markers show the shortest and the

longest contraction durations in each person. The difference in contraction duration is 0.03 s in the healthy individual and 0.12 s in the LQTS patient and is consistent with the mechanical dispersion of contraction (Eur Heart J. 2009).

Strain by speckle tracking echocardiography

Strain is defined as the fractional change of tissue length and is expressed in a dimensionless unit either as percent shortening (negative values) (Figure 4) or percent lengthening (positive values).

In Paper 2, 3 and 4 strain measurements were obtained by speckle tracking echocardiography as previously described (38). Briefly, speckles are results of the ultrasound technique. The software algorithm tracks the speckles from frame to frame and calculates the distance between the speckles during the heart cycle. These distance measurements provide accurate assessment of myocardial contraction during the cardiac cycle. 2-D grayscale images were acquired in apical 4 chamber, 2 chamber and long axis views. Figure 4 displays strain curves from a healthy individual.

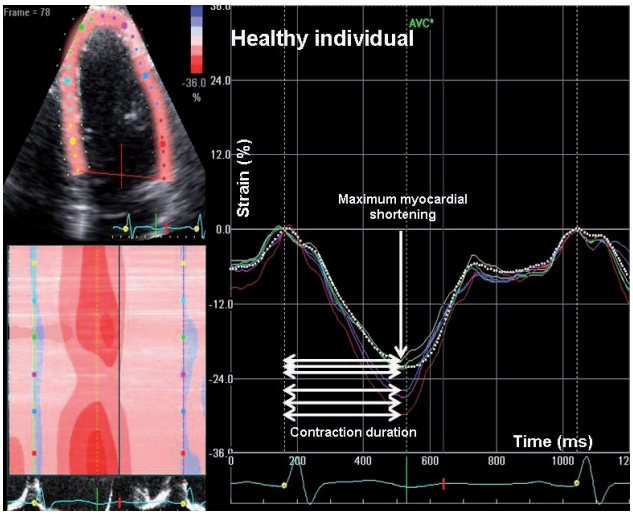

Figure 4. Speckle tracking longitudinal strain curves from 6 segments in apical 4 chamber view from a healthy individual with synchronous ECG recording below. Segment contraction (shortening) starts during QRS and reaches maximum shortening (white vertical arrow) at the end of the ECG T-wave.

AVC (green vertical line) indicates timing of aortic valve closure. In diastole, segment is lengthening. Global strain was defined as mean myocardial shortening from a 16 LV segments model. Contraction duration was defined as the time from ECG onset Q/onset R wave to maximum myocardial shortening (time lines). Mechanical dispersion was calculated as standard deviation of contraction duration from 16 LV segments.

In Paper 2, we assessed longitudinal and circumferential strains. The addition of circumferential strain in Paper 2 was performed as an indirect measure of transmural differences in myocardial contraction. The subendocardium mainly consists of longitudinal myocardial fibers while the mid-myocardium mainly consists of circumferentially oriented fibers (42). Due to this myocardial fiber geometry, strain measurements are able to indirectly discriminate differences between subendocardial and mid-myocardial layers. Contraction durations by longitudinal strain therefore mainly measure subendocardial myofiber contraction while contraction durations by circumferential strain measure mid-mycoardial contraction. Considering this myocardial fiber orientation, we used differences in longitudinal and circumferential contraction duration as an indirect measure of transmural mechanical dispersion.

We assessed the following parameters at frame rate of 76±18 frames/s:

1. Maximum myocardial shortening (Figure 4).
2. Global strain, calculated as the average of longitudinal maximum myocardial shortening from 16 LV segments.
3. Time from ECG onset Q (onset R wave if Q wave was absent) to maximum myocardial shortening defined as contraction duration (Figure 4).
4. Standard deviation of the 16 longitudinal measured and 6 circumferential measured contraction durations was calculated as parameters of mechanical dispersion.
5. Time difference between the longest and the shortest contraction duration was defined as delta contraction duration in longitudinal and circumferential directions.

6. Transmural mechanical dispersion was expressed by the time difference in longitudinal and circumferential contraction durations of the 6 basal LV segments (Figure 5).

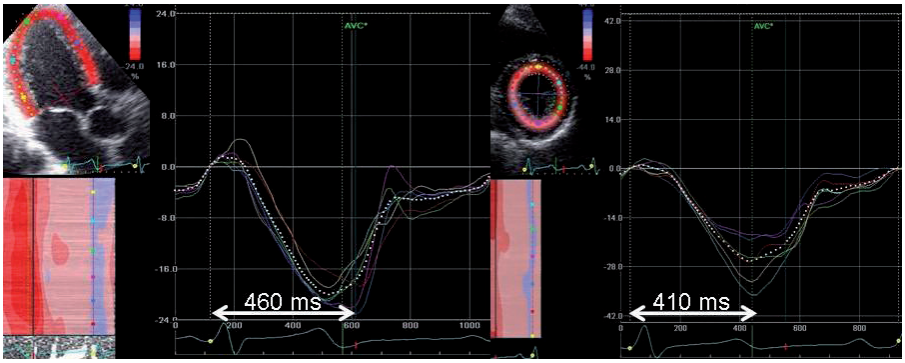

Figure 5. Longitudinal (left panel) and circumferential (right panel) strain in a symptomatic LQTS patient by speckle tracking echocardiography. Longitudinal strain mainly measures subendocardial myofibers, while circumferential strain mainly measures mid-myocardial fibers. Mean longitudinal strain was longer compared to mean circumferential strain in this symptomatic LQTS patient, indicating transmural mechanical dispersion.

In post-MI patients in Paper 3, following parameters were assessed by longitudinal strain by speckle tracking technique with frame rate at 63±23 frames/s:

1. Contraction duration as the time from start of Q/R wave on ECG to maximum myocardial shortening (Figure 4)

2. Mechanical dispersion was calculated from contraction durations from a 16 LV segments model.

3. Global LV strain was obtained by averaging all segmental values for maximum shortening in a 16 segment model (Figure 4).

4. The difference between the longest and the shortest contraction duration in each individual was defined as delta contraction duration

In Paper 4, peak systolic myocardial strain by 2D speckle tracking echocardiography was assessed in 16 LV segments and averaged to LV global longitudinal strain in ARVC patients (Figure 4). Additionally, peak systolic strain from 3 right ventricular (RV) free wall segments was averaged as a measure of RV function (RV strain) (Figure 6). Contraction duration was measured as time from onset R on ECG to maximum LV and RV shortening by strain. Standard deviation of contraction duration was calculated as mechanical dispersion, in a 16 LV segment and a 6 RV segment model.

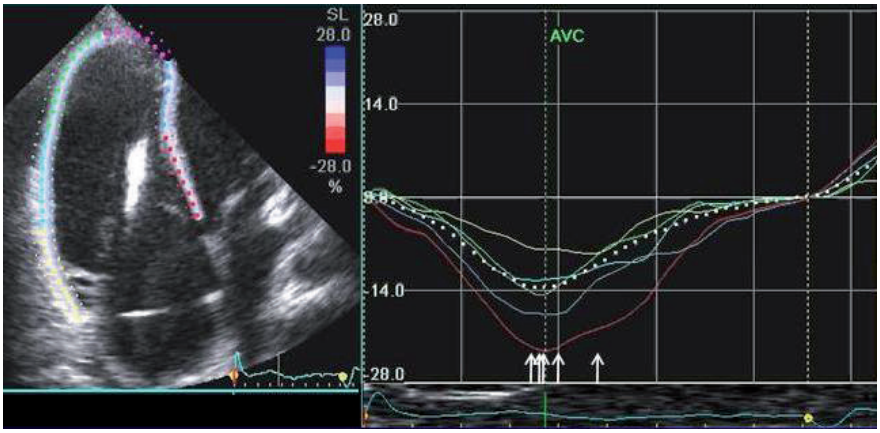

Figure 6. Strain curves from a dilated right ventricle in an ARVC patient from apical 4 chamber view. Vertical arrows indicate the timing of maximum myocardial shortening in each RV segment and are consistent with pronounced RV mechanical dispersion.

Reproducibility and feasibility

Paper 1: The intra- and inter observer variability of PEV measurements demonstrated an intraclass correlation coefficient of 0.92 (95% CI 0.84-0.96) and 0.79 (95% CI 0.68-0.86), respectively and for contraction duration measurements 0.97 (95% CI 0.92- 0.99) and 0.92 (95% CI 0.72- 0.98) respectively.

Paper 2: Myocardial strain could be assessed in 98% of the myocardial segments in LQTS mutation carriers and in 94% of the subjects in the healthy individuals. The primary analysis was done by a single observer and

repeated in a blinded fashion. For contraction duration intra-, inter observer and test retest intraclass correlation were 0.96, 0.96 and 0.87, respectively and for mechanical dispersion 0.98, 0.89, 0.79, respectively. The corresponding QTc and QTc dispersion test retest intraclass correlation were 0.82 and 0.67, respectively.

Paper 3: Strain parameters could be assessed in 95% of the myocardial segments in the study group and in 91% of the subjects in the control group. Time measurements included 88% of the segments in the infarcted patients with ICD. Intra observer and inter observer variability were 0.98 and 0.98, respectively, for strain measurements and 0.86 and 0.81 for time measurements.

Statistical analyses

Continuous data were presented as mean ± standard deviation or as median (range). Comparisons of means were analyzed by unpaired t test or ANOVA with the Bonferroni correction for multiple comparisons (SPSS 15.0). For comparisons within the same patient, paired t test was used. Kruskal Wallis test was performed for non-parametric variables. Proportions were compared with the use of Chi square or Fisher's exact test. Cox regression analysis was used in Paper 3 to identify predictors of the outcome arrhythmia requiring appropriate ICD treatment. Hazard ratios and 95% confidence intervals (CI) were calculated. The multivariate analysis was performed by including significant variables from the univariate model ($p<0.05$) in addition to age and EF which were forced in. A close relationship was observed between mechanical dispersion and delta contraction duration and therefore only dispersion was included in the multivariate analysis. Kaplan-Meier analysis was used to create freedom-from-arrhythmia survival curves. Receiver operating characteristics (ROC) analyses were performed in all 4 papers. The value closest to the upper left corner of the ROC curve was used to define cut off value for optimal sensitivity and specificity for the ability of the parameters contraction duration and mechanical dispersion to identify arrhythmic events. Reproducibility was expressed as intraclass correlation coefficient. P-values less than 0.05 were considered significant.

Summary of results

Paper 1

LQTS mutation carriers (n=73) were compared with 20 healthy individuals and 18 otherwise healthy individuals on beta blocker therapy with respect to cardiac contraction duration and mechanical dispersion measured by tissue Doppler imaging.

Contraction duration was significantly longer in symptomatic LQTS mutation carriers compared to asymptomatic carriers and healthy individuals (460±60ms vs. 400±60ms and 360±40ms, $p<0.001$). The correlation between contraction duration and QTc was significant ($R=0.43$, $p<0.001$). In contrast to healthy individuals, LQTS mutation carriers showed contraction durations that exceeded the time to aortic valve closure. Otherwise healthy individuals on beta-blocker therapy did not have prolonged contraction duration compared to healthy individuals (380±40ms vs. 360±40ms, ns). Mechanical dispersion, assessed as standard deviation of contraction duration, was significantly greater in LQTS mutation carriers compared to healthy individuals (40±20ms vs. 14±13ms, $p<0.001$) and compared to otherwise healthy individuals on beta blocker therapy (40±20ms vs. 24±17ms, $p=0.005$). In addition, mechanical dispersion was significantly greater in symptomatic compared to asymptomatic LQTS mutation carriers (48±18ms vs. 31±19ms, $p=0.001$).

A marked post ejection shortening velocity (PEV) was observed in LQTS mutation carriers and was significantly greater than PEV found in healthy individuals (1.8±1.4cm/s vs. -0.2±0.7cm/s, $p<0.001$). In addition, the maximum PEV in symptomatic LQTS mutation carriers was greater than in asymptomatic LQTS mutation carriers (2.3±1.3cm/s vs. 1.1±1.3cm/s, $p=0.001$).

By ROC analysis, contraction duration identified mutation carriers with a history of cardiac events with better specificity and sensitivity than QTc did (Figure 7).

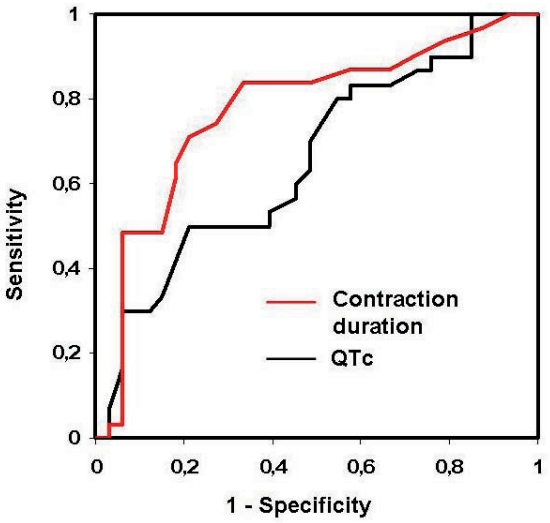

Figure 7. ROC curves of cardiac events (documented arrhythmia, syncope or aborted cardiac arrest) in 64 single LQTS mutation carriers (33 symptomatic and 31 asymptomatic). Myocardial contraction duration shows higher ability to identify cardiac events compared to QTc. Area under curve 0.77 (95% CI 0.65-0.89) vs. 0.66 (95% CI 0.52-0.79).

Paper 2

101 LQTS mutation carriers (53 asymptomatic and 48 symptomatic) were investigated by myocardial strain in longitudinal and circumferential directions in order to detect regional myocardial contraction abnormalities. 35 healthy individuals served as control group.

Symptomatic LQTS mutation carriers had longer QTc compared to asymptomatic mutation carriers (495±50ms vs. 460±30ms, $p<0.001$).

Mean longitudinal contraction duration was longer in LQTS mutation carriers compared to healthy individuals (445±45ms vs. 390±40ms, $p<0.001$) and longer in symptomatic compared to asymptomatic LQTS mutation carriers (460±40ms vs. 425±45ms, $p<0.001$).

In symptomatic LQTS patients, mean contraction duration measured by longitudinal strain was significantly longer compared to circumferential reflecting transmural dispersion (460±45ms vs. 445±45ms, $p=0.008$), indicating transmural mechanical dispersion. This time difference was present a majority of LV segments and most evident in LQT2 and patients with Jervell and Lange-Nielsen syndrome. In asymptomatic LQTS mutation carriers and healthy individuals there were no significant differences in mean contraction duration measured by longitudinal compared to circumferential strain ($p=0.31$ and $p=0.99$, respectively), indicating absence of transmural mechanical dispersion.

Longitudinal mechanical dispersion was more pronounced in LQTS patients compared to healthy individuals (36±15ms vs. 20±7ms, $p<0.001$) (Figure 8). In addition, mechanical dispersion was significantly greater in symptomatic LQTS mutation carriers compared to asymptomatic in longitudinal (45±13ms vs. 27±12ms, $p<0.001$) and circumferential directions (46±22ms vs. 26±21ms, $p<0.001$). QTc dispersion was prolonged in symptomatic LQTS mutation carriers compared to asymptomatic (56±23ms vs. 48±17ms, $p=0.04$). There was a moderate, but significant correlation between mechanical dispersion and QTc dispersion ($R=0.30$, $p=0.007$)

As determined by ROC analysis, longitudinal mechanical dispersion could better discriminate between LQTS mutation carriers with and

without cardiac events (syncope, documented arrhythmia, aborted cardiac arrest) compared to QTc (Area under the curve for mechanical dispersion 0.87 (95%CI 0.79-0.94) versus QTc 0.71 (95%CI 0.61-0.81) (p<0.01).

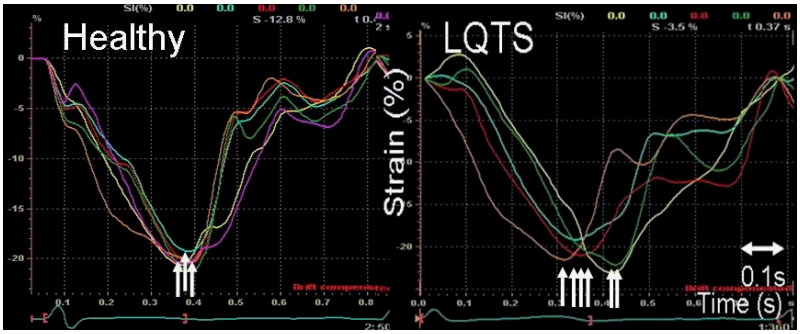

Figure 8. Myocardial strain curves from 6 different locations in a healthy individual (left panel) and a LQTS patient (right panel). White arrows indicate timing of maximum myocardial shortening. Mechanical dispersion was calculated as the standard deviation from 12 different contraction durations. The LQTS patient shows more pronounced mechanical dispersion compared to the healthy individual.

Paper 3

Mechanical dispersion was assessed in 44 post-MI patients with ICD according to primary prevention criteria and in 41 post-MI patients with ICD according to secondary prevention criteria. Thirty-eight (45%) ICD patients experienced one or more episodes with sustained VT or VF requiring appropriate ICD therapy (ATP or shock) while 47(55%) had no sustained arrhythmia during 2.3(0.6,5.5) years of follow up. Post-MI patients without ICD indication (n=20) and healthy individuals (n=23) were included for comparison.

Mechanical dispersion was significantly more pronounced in those with arrhythmias compared to those without (85±29ms vs. 56±13ms, $p<0.001$) (Figure 9). By Cox regression, mechanical dispersion was a strong and independent predictor of arrhythmias requiring ICD therapy (per 10ms increase of mechanical dispersion: HR 1.25, 95% confidence interval (CI) 1.1 to 1.4, $p<0.001$). By Kaplan Meier analysis, ICD patients with mechanical dispersion >70ms showed more frequent arrhythmic events than ICD patients with dispersion <70ms (Log Rank test, $p<0.001$). In ICD patients with EF>35%, mechanical dispersion was more pronounced in those who experienced arrhythmia (n=22) compared to those without (n=21) (80± 27ms vs. 61±12ms, $p=0.01$). Control post MI patients without ICD indication had slightly pronounced mechanical dispersion compared to healthy individuals (45±15ms vs. 22±10ms, $p<0.01$).

Global strain showed better LV function in those without recorded arrhythmias (-14.0±4.0% vs. -12.0±3.0%, $p=0.05$), while EF did not differ (44±8% vs. 41±5%, $p=0.23$).

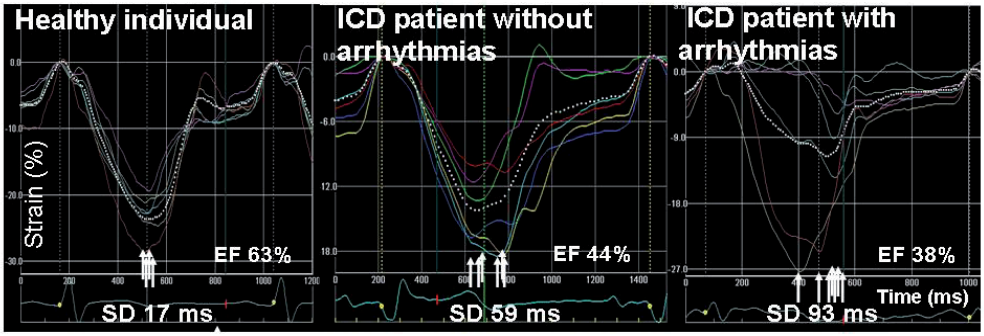

Figure 9. Mechanical dispersion by strain echocardiography in a healthy individual and ICD patients without and with follow up arrhythmias.
Speckle tracking longitudinal strain curves in 4-chamber view from a healthy individual (left panel), a post-MI ICD patient without arrhythmic events (center panel) and a post-MI ICD patient with recurrent arrhythmias (right panel). White arrows indicate timing of maximum myocardial shortening in each segment. Myocardial shortening is reduced in the ICD patients and the timing of shortening is dispersed compared to the healthy individual. The dotted line represents the average myocardial shortening for each individual. SD = standard deviation of time to maximum myocardial shortening. (J Am Coll Cardiol Img 2010; 3:247-56)

Paper 4

Mechanical dispersion and strain in RV and LV were assessed in 36 ARVC patients, in 23 asymptomatic ARVC mutation carriers and in 30 healthy individuals.

Mechanical dispersion was more pronounced in ARVC patients with arrhythmias in RV and LV compared to asymptomatic mutation carriers and healthy individuals (Table 1). Importantly, mechanical dispersion was more pronounced in asymptomatic mutation carriers compared to healthy individuals in both RV and LV, indicating sub clinical ventricular involvement. RV and LV strains were reduced in ARVC patients compared to asymptomatic mutation carriers and healthy individuals (Table 1). Reduced RV and LV strain were significantly correlated in ARVC patients, indicating biventricular disease ($R=0.84$, $p<0.05$). RV and LV function in asymptomatic mutation carriers were within normal range, but significantly reduced compared to healthy individuals.

Four study patients initially were admitted to hospital due to life threatening arrhythmias (2 with VF and 2 with VT). Despite normal conventional echocardiographic and MRI findings at admittance, all 4 had significant increase in mechanical dispersion in RV (48±11ms) and LV (52±11ms) compared to healthy individuals (both $p<0.001$). Three of them had an ARVC related mutation and 1 patient progressed subsequently to typical ARVC phenotype.

Table1. Echocardiographic results in 36 ARVC patients, 23 asymptomatic ARVC mutation carriers and 30 healthy individuals.

	Healthy individuals (n=30)	Asymptomatic mutation carriers (n=23)	ARVC patients with arrhythmias (n=36)	P
EF (%)	64±5	63±4	57±14*	<0.01
LV strain (%)	-23±2	-20±2*	-16±5*·**	<0.001
RV strain (%)	-28±5	-24±5*	-19±7*·**	<0.001
LV Dispersion (ms)	22±8	42±13*	64±25*·**	<0.001
RV Dispersion (ms)	15±8	33±20*	53±25*·**	<0.001

*Mean±SD. Right column shows P-values for ANOVA test. Flags for significance are obtained from the post hoc pair-wise comparison using the Bonferroni correction. *p<0.05 compared with healthy individuals. **p<0.01 compared with asymptomatic mutation carriers. ANOVA, analysis of variance; EF, ejection fraction; RV, right ventricular; LV, left ventricular.*

Discussion

This thesis introduces new principles in risk assessment of life threatening arrhythmias in patients with susceptibility for ventricular arrhythmia. LQTS-, ARVC- and post-MI patients with recorded arrhythmias showed pronounced mechanical dispersion assessed by echocardiographic techniques. In all studies, mechanical dispersion was a marker of arrhythmic evens. These findings indicate that myocardial electrical abnormalities present in these patients may be visualized as mechanical dispersion by accurate echocardiographic techniques.

Electromechanical interactions in LQTS

As the QT interval on the surface ECG represents the summation of action potentials in ventricular myocytes, QT prolongation implies action potential prolongation in at least some portions of the ventricle. A prolongation of the action potential duration is associated with an increase in the tension developed by the ventricular muscle leading to a prolonged contraction (43-45). In Paper 1 and 2, prolonged contraction duration was demonstrated in LQTS mutation carriers compared to healthy individuals and in symptomatic LQTS mutation carriers compared to asymptomatic. The contraction duration in LQTS mutation carriers exceeded the time to aortic valve closure. This indicated myocardial contraction after aortic valve closure, which may be a result of an inhomogeneous end of contraction not sufficient to maintain the opening of the aortic valve.

These findings were in accordance with sporadic but consistent reports during the past 20 years that electrical alterations in LQTS patients have mechanical consequences (12, 13, 46, 47). The specific patterns of myocardial contraction abnormalities described in this thesis may depend on the concomitant electrical disorder in these patients.

Mechanical dispersion in LQTS

Findings from LQTS patients have implicated a specific role for dispersion of electrical repolarization in ventricular arrhythmogenesis (8, 48). Dispersion of repolarization can occur between apex and base i.e. longitudinally

and transmurally and facilitate the generation of Torsade de Pointes arrhythmia (8). The measurement of QT dispersion on ECG as an indicator of dispersion of ventricular repolarization was presented as a promising tool in risk stratification of arrhythmias two decades ago (49). However, the method has not achieved the clinical value as initially expected due to challenges in T-wave definition and poor reproducibility (50). QTc dispersion in this study showed significant differences between LQTS mutation carriers with and without arrhythmic events. The moderate but significant correlation to mechanical dispersion supported that our echocardiographic findings may reflect electrical dispersion.

With the methods presented in this thesis, we were able to quantify longitudinal (between apex and base) and inter regional mechanical dispersion (between interventricular septum, lateral wall, anterior and posterior wall). In Paper 2, we were also able to provide an indirect measure of mechanical transmural dispersion, when comparing duration of longitudinal strain (subendocardial fibers) with circumferential strain (mid-myocardial fibers). Contraction duration by longitudinal strain (subendocardial layers) was significantly longer than by circumferential strain (mid myocardial layers) in symptomatic LQTS patients. These findings indicate a transmural mechanical dispersion in symptomatic LQTS patients which was not present in asymptomatic and healthy individuals. These mechanical findings are in accordance with previous electrical LQTS models reporting longest APD in Purkinje cells and M cells which are located in the subendocardium and mid myocardium (5, 10, 51). Purkinje cells are found in the His bundle, bundle branches and cover much of the endocardium (51). The transmural mechanical dispersion presented in Paper 2 may represent the transmural electrical dispersion of repolarization which is shown to be present in LQTS models and which is suggested to be a strong arrhythmogenic factor (8). Despite the limited number of genotype subgroup participants, transmural mechanical dispersion was pronounced in LQT2 patients and patients with JLNS. These findings may indicate genotype specific differences in electrical dispersion and are in accordance with the higher arrhythmic risk in patients with these genotypes (2, 52).

In summary, Paper 1 and 2 demonstrated that mechanical dispersion can be assessed by TDI and strain echocardiography as regional differences in contraction duration throughout the LV. Importantly, prolonged and dispersed myocardial contraction was associated with a higher risk of cardiac arrhythmias in LQTS mutation carriers.

Mechanical dispersion and LV function in infarcted tissue

There is ample evidence from different cardiac disease models, including heart failure (53), ischemia (28) and infarction (29, 54) that increases in dispersion of conduction velocity result in susceptibility to arrhythmias (9, 53, 54). These electrical abnormalities will presumptively lead to changes in myocardial function. Assessing the extent of electrical dispersion in the individual patient has so far been difficult (53). In Paper 3, mechanical dispersion was pronounced in post-MI ICD patients with recurrent ventricular arrhythmias compared to ICD patients without further arrhythmias. These findings support the idea that tissue heterogeneity in and around scarred myocardium lead to a dispersed myocardial contraction and is associated with risk of arrhythmic events.

In control post-MI patients with preserved EF and without arrhythmias, mechanical dispersion was significantly lower compared to ICD patients with recorded arrhythmias, and tended to be lower compared to ICD patients without arrhythmic events. These findings demonstrated presence of mechanical dispersion in all post-MI patients and support the assumption that the extent of mechanical dispersion is important in arrhythmogenesis.

Earlier echocardiographic studies have observed that an EF of ≤40% serves as the threshold for identifying high-risk individuals (55, 56). However, EF has reduced sensitivity in predicting sudden death; less than 50% of patients with prior MI who die suddenly have EF below 30% (24, 57). Speckle based strain has shown to be a robust technique for assessment of LV function and a recent study has demonstrated that speckle tracking strain is superior to EF for assessment of myocardial function post-MI (38). In Paper 3, global strain discriminated between those with and without arrhythmic events in post-MI patients with EF>35%. This finding suggests that global strain might become a useful tool for

risk stratification in post-MI patients with relatively preserved LV function. EF, however, failed to identify arrhythmic events in post-MI patients with EF>35%. Future trials should investigate if mechanical dispersion and global strain can be used to select additional patients for ICD therapy among the majority of post-MI patients with relatively preserved EF in whom current ICD indications fail.

Mechanical dispersion and biventricular dysfunction in ARVC

Risk stratification of ventricular arrhythmias in so far asymptomatic ARVC mutation carriers is difficult. Paper 4 demonstrated that mechanical dispersion was closely related to ventricular arrhythmias in patients with ARVC. Increased mechanical dispersion in both ventricles was present in asymptomatic mutation carriers, indicating sub clinical myocardial alterations. Importantly, pronounced mechanical dispersion was also present in individuals who had experienced arrhythmias in the early stages of ARVC and in whom no structural alterations assessed by conventional echocardiography and MRI could be assessed. These findings suggest that mechanical dispersion may be a marker of arrhythmic events and help risk stratification in so far asymptomatic ARVC mutation carriers. Mechanical dispersion and myocardial strains demonstrated subclinical myocardial involvement in these individuals. Longitudinal follow up studies are required to assess if these methods can provide added value in arrhythmia risk stratification in asymptomatic ARVC mutation carriers.

Furthermore, Paper 4 demonstrated frequent and early LV involvement in ARVC which support recent reports of ARVC as a biventricular disease (58). Biventricular impairment is probably a result of biventricular ARVC affection, but mutual dependency of RV and LV hemodynamics may be considered. In patients with overt ARVC, strain echocardiography may be a useful tool for quantification of right and left sided myocardial dysfunction.

Mechanical dispersion in LQTS, ARVC and post-MI patients

In this thesis, mechanical dispersion was demonstrated in LQTS patients, ARVC patients and in post-MI patients and was shown to be a marker of recurrent ventricular arrhythmias. The mechanisms for arrhythmias in LQTS, ARVC and in infarcted myocardial tissue are different, but have similarities regarding electrical dispersion. In LQTS patients, inherited ion channel defects result in prolonged APD. Inhomogeneous prolongation of APD in LQTS result in dispersed electrical repolarization, which is regarded as a major arrhythmia mechanism. In ARVC patients, mechanisms of arrhythmias are probably stage dependent, but electrical dispersion has been considered to be of importance in early and later stages of the disease (22, 23). In post-MI patients delayed start of ventricular activation in scarred myocardium leads to a dispersed recovery of excitability (29), finally resulting in dispersed electrical repolarization. One might therefore speculate that electrical dispersion may be regarded as the final common pathway of arrhythmia mechanism in all three conditions.

The extent of mechanical dispersion appeared most pronounced in post-MI patients, followed by ARVC patients and less pronounced in LQTS patients. These differences were probably a result of the concomitant contractile impairment in infarcted tissue and presence of fibrosis in ARVC which were not present in LQTS patients as confirmed in this thesis. Post-MI patients and ARVC patients had significantly impaired myocardial function, while LQTS patients had normal EF and strain amplitudes. Contractile impairment will pronounce mechanical dispersion. The ranges and values of mechanical dispersion which are related to increased arrhythmic risk will therefore not necessarily be interchangeable between different myocardial diseases.

Methodology: Tissue velocities by Doppler and strain by speckle tracking echocardiography

In Paper 1, TDI measurements were used for assessment of contraction duration and mechanical dispersion. A limitation of TDI is marked

angle dependency, which makes it sensitive to malalignment between the principle direction of myocardial shortening and the Doppler beam. In order to avoid problems related to angle dependency of the TDI technique, we excluded velocity curves obtained from apical segments. TDI technique is appropriate for time measurements. The high temporal resolution facilitates high accuracy in time measurements. The reason for using TDI myocardial velocities in Paper 1 was that this technique is widely in use. However, the TDI velocity method in Paper 1 was not designed to distinctly quantify separate regions of the myocardium for comparison. In Paper 2-4, myocardial strain measurements were used. Myocardial strain measurements can identify myocardial dysfunction of more regional character, and can accurately assess myocardial shortening in a distinct part of the ventricle. Speckle tracking technique as used in these papers is attractive and robust in use. Compared to the TDI technique, speckle tracking is ultrasound beam angle independent and easier and faster to use. Reproducibility and feasibility studies in this thesis including velocity and strain measurements were satisfying.

This thesis shows that echocardiographic evaluation of mechanical dispersion can add important information in patients with susceptibility for ventricular arrhythmias. Importantly, mechanical dispersion should be used in addition to current risk stratification tools in order to include further patients for therapy. The studies in this thesis were not designed to provide results which could exclude patients from current therapy.

Limitations

The association between mechanical dispersion and electrical dispersion should be studied in experimental studies.

Paper 1 and 2 did not provide data that actually demonstrated that asymptomatic LQTS mutation carriers with prolonged contraction duration and pronounced mechanical dispersion were more likely to develop arrhythmias than those without. This requires prospective studies where asymptomatic untreated patients are followed for an adequate period of time, which is difficult for ethical reasons.

Arrhythmia prediction by mechanical dispersion in post-MI patients in Paper 3 must be interpreted with respect to the fact that all patients fulfilled current guidelines for ICD therapy and may not be appropriate in patients not fulfilling current ICD indications. Further prospective trials including post-MI patients not fulfilling ICD indications are required.

Main conclusions

Novel echocardiographic methods add important information in risk stratification of ventricular arrhythmias in patients at risk.

1. LQTS patients showed prolonged myocardial contraction duration assessed with TDI velocities and strain echocardiography. LQTS patients had more pronounced mechanical dispersion compared to healthy individuals. LQTS patients with arrhythmias had more pronounced mechanical dispersion than asymptomatic LQTS mutation carriers. Mechanical dispersion was superior to QTc in identifying arrhythmic events and may provide added value in risk stratification of LQTS mutation carriers.
2. Symptomatic LQTS mutation carriers had longer contraction duration in the subendocardial layer compared to the mid layer of the ventricular wall, indicating transmural mechanical dispersion which was not present in asymptomatic mutation carriers and in healthy individuals. Transmural mechanical dispersion was evident in patients with LQT2 and Jervell and Lange-Nilsen syndrome and associated with ventricular arrhythmias.
3. Post-MI patients at risk for cardiac arrhythmias had increased myocardial mechanical dispersion by strain echocardiography. Mechanical dispersion was a strong and independent predictor of arrhythmic events in post-MI patients. LV global strain discriminated between post-MI patients with and without arrhythmic events in those with relatively preserved EF, while EF did not differ. Mechanical dispersion and global strain may be useful for including more patients after MI for ICD therapy.
4. Mechanical dispersion was pronounced in ARVC patients and was related to ventricular arrhythmias. The findings were present in both right and left ventricle supporting that ARVC is a biventricular disease. Mechanical dispersion was present in asymptomatic mutation carriers with no signs of the disease on MRI or traditional echocardiography. Follow up studies are needed to evaluate mechanical dispersion as a risk stratification tool in ARVC mutation carriers.

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Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome

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Aims The aim of this study was to investigate whether prolonged and dispersed myocardial contraction duration assessed by tissue Doppler imaging (TDI) may serve as risk markers for cardiac events (documented arrhythmia, syncope, and cardiac arrest) in patients with long QT syndrome (LQTS).

Methods and results Seventy-three patients with genetically confirmed LQTS (nine double- and 33 single-mutation carriers with previous cardiac events and 31 single-mutation carriers without events) were studied. Myocardial contraction duration was prolonged in each group of LQTS patients compared with 20 healthy controls ($P < 0.001$). Contraction duration was longer in single-mutation carriers with previous cardiac events compared with those without (0.46 ± 0.06 vs. 0.40 ± 0.06 s, $P = 0.001$). Prolonged contraction duration could better identify cardiac events compared with corrected QT (QTc) interval in single-mutation carriers [area under curve by receiver-operating characteristic analysis 0.77 [95% confidence interval (95% CI) 0.65–0.89] vs. 0.66 (95% CI 0.52–0.79)]. Dispersion of contraction was more pronounced in single-mutation carriers with cardiac events compared with those without (0.048 ± 0.018 vs. 0.031 ± 0.019 s, $P = 0.001$).

Conclusion Dispersion of myocardial contraction assessed by TDI was increased in LQTS patients. Prolonged contraction duration was superior to QTc for risk assessment. These new methods can easily be implemented in clinical routine and may improve clinical management of LQTS patients.

Keywords Long QT syndrome • Echocardiography • Ventricular arrhythmia • Myocardial contraction • Dispersion

Introduction

The long QT syndrome (LQTS) is a genetic disorder characterized by prolonged ventricular repolarization that predisposes to life-threatening arrhythmias.[1] The pathophysiology behind the arrhythmias in LQTS is not precisely defined. Possible mechanisms include early after-depolarizations (EADs) and dispersion of myocardial repolarization.

Fifty years after its initial description,[2–4] approaches for risk stratification are insufficiently defined. Risk stratification today is based on history of syncope, genotype, gender, and corrected QT (QTc) interval.[1,5] Prolonged QTc is a marker of prolonged action potential duration which is associated with a prolonged left ventricular (LV) contraction.[6–8] Electrocardiogram (ECG) has limited abilities to detect regional differences in LV electrical pattern. A relationship between motion abnormalities of the LV

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assessed by echocardiography and syncope or cardiac arrest in LQTS patients was first indicated by Schwartz and colleagues.[9,10] Tissue Doppler imaging (TDI) has been established as a clinical method for the quantification of regional myocardial function.[11] The diagnostic value of this new modality has not been previously described in LQTS patients.

The objective of this study was to determine whether myocardial velocities, time-intervals, or strains by TDI could be a tool for identifying high-risk individuals in LQTS patients. High risk was defined as patients with a previous cardiac event, i.e. documented arrhythmia, syncope, or cardiac arrest. Our hypothesis was that prolonged action potentials will cause a prolonged myocardial contraction that can be assessed by TDI. Furthermore, we hypothesized that myocardial mechanical dispersion can be assessed as heterogeneity in the regional myocardial contraction duration by TDI.

Methods

Long QT syndrome patients

Seventy-three patients with molecularly defined LQTS were included in this study (*Figure 1*). None of the LQTS patients had structural heart disease of other origin or were ventricularly paced. All 73 LQTS mutation carriers were genotyped: 44 LQT1, 18 LQT2, 1 LQT3, 1 LQT5, and nine double-mutation carriers. Double-mutation carriers were considered a separate category and were analysed separately.

Long QT syndrome single-mutation carriers

Sixty-four patients were single-mutation carriers of an LQTS-associated mutation. Of the single-mutation carriers, 33 (52%) had a history of documented arrhythmia, syncope, or cardiac arrest, here defined as 'symptomatic'. All symptomatic and three asymptomatic single-mutation carriers received therapy with beta-blockers ($n = 36$). In addition to beta-blocker therapy, three single-mutation carriers were treated with an ICD and three with atrial pacemaker.

In addition, six single-mutation carriers were studied with ECG and echocardiography but deemed ineligible for inclusion. One of these six was an LQT1 patient who received chemotherapy owing to malignant disease and developed cardiomyopathy with reduced LV function. Five asymptomatic mutation carriers <15 years of age were ineligible for inclusion. We could not exclude future cardiac events in these young individuals and their status as asymptomatic in this study would therefore be inaccurate.

Long QT syndrome double-mutation carriers, Jervell and Lange-Nielsen syndrome

Nine patients were double-mutation carriers of an LQTS-associated mutation and had clinically Jervell and Lange-Nielsen syndrome (JLNS) with additional deafness. All JLNS patients had experienced repeated cardiac events and were treated with beta-blockers. In addition, one JLNS patient was treated with left sympathetic denervation, two with an ICD, and three with atrial pacemaker.

Control groups

Healthy individuals

Twenty healthy individuals were age- and sex-matched and recruited from hospital staff. All had normal clinical examination, ECG, QTc, and echocardiography.

Individuals on beta-blocker therapy

Since 64% of the LQTS patients were on beta-blocker therapy, we included 18 individuals on beta-blocker therapy for comparison. They were treated with beta-blockers for suspected angina pectoris from the referral institution ahead of an elective coronary angiography. They were included in our beta-blocker control group after findings of a normal coronary angiography at our hospital. In addition, normal findings were required for the clinical examination, ECG, QTc, and echocardiography. Beta-blocker treatment was discontinued in all these patients after the examination at our hospital.

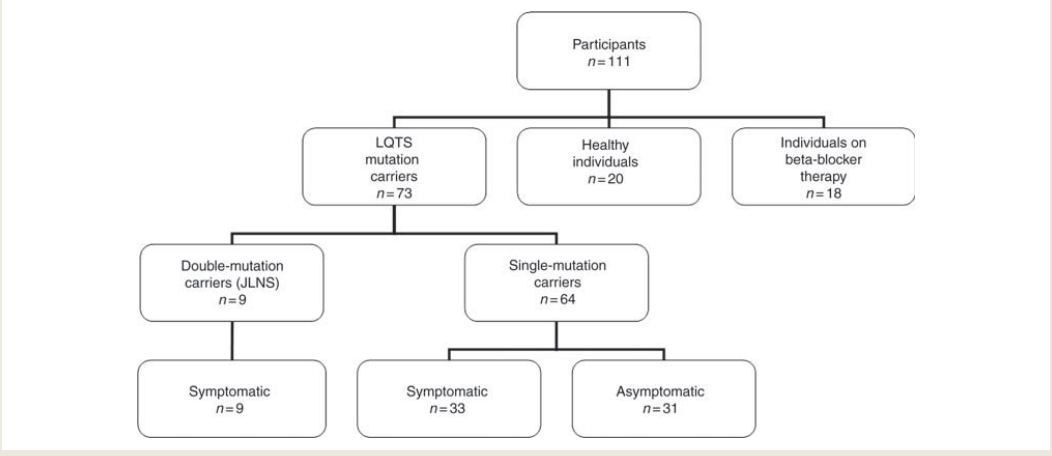

Figure 1 Algorithm of study participants. The groups of healthy individuals and individuals on beta-blocker therapy represent the control groups.

Written informed consent was given by all participants. The study was approved by the Regional Committee for Medical Research Ethics.

Electrocardiogram

Twelve-lead ECG was obtained in all participants, either before or after echocardiography. The QT interval was corrected for heart rate using Bazett's formula.[12]

Echocardiographic studies

The echocardiographic studies were performed using Vivid 7 (GE Healthcare, Horten, Norway) and analysed with commercially available software (EchoPAC®, GE). By conventional 2D echocardiography, we assessed LV ejection fraction *ad modum* Simpson. Systolic time interval was assessed by Doppler flow velocity measurement as the time from start of R on ECG to aortic valve closure.

Tissue Doppler imaging

Two-dimensional TDI recording of the LV was obtained from the basal and mid-segments from apical four-chamber, two-chamber, and long-axis views. Three cycles were analysed and the image frame rate obtained in this study was 124 ± 29 frames/s. The following parameters from TDI were assessed:

(i) Peak ejection velocity.
(ii) Peak myocardial velocity after aortic valve closure—post-ejection velocity (PEV). PEV was defined as the peak of the upstroke of the biphasic spike after ejection. In individuals without post-systolic shortening, this spike can occur below the zero line (*Figure 2*).
(iii) Maximum PEV in absolute value, negative or positive, was measured and the anatomical location was noted in each participant.
(iv) Myocardial contraction duration was measured in the basal septal segment and defined as the time from start of R on ECG to end of PEV (zero-crossing) if positive PEV was present. If no positive PEV was present, contraction duration was defined as the time from start of R on ECG to zero-crossing of the decreasing velocity slope in end-systole (*Figure 2*).
(v) Contraction duration of the basal segment of the six LV wall positions was measured and the standard deviation of these values calculated as a parameter of mechanical dispersion of contraction (*Figure 3*).
(vi) In diastole, we measured the time from start of R to onset of E′ and peak E′.
(vii) Contraction duration was measured in strain traces as the time from start of R on ECG to peak negative strain (*Figure 2*).

Efforts were made to ensure good image quality in each patient. TDI parameters could be assessed in 98% of the myocardial segments in LQTS mutation carriers and in 94% of the subjects in the other groups. The primary analysis was done unblinded by a single observer and repeated in a blinded fashion 4 months later (K.H.H.). All analyses were repeated by an independent observer (T.E.), blinded to patient identity and other data. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Statistical analyses

Data were presented as mean ± standard deviation. Comparisons of means were analysed by ANOVA with the Bonferroni *post hoc* correction for multiple comparisons (SPSS 15.0). Receiver-operating characteristic (ROC) curves were constructed to determine the sensitivity and specificity of the parameters—QTc, myocardial contraction duration, and PEV—to identify cardiac events (documented arrhythmia, syncope, or cardiac arrest) in LQTS single-mutation carriers. For contraction duration and PEV, the optimal cut-offs were defined as the value of the ROC curve which was closest to the upper left corner (*Figure 4*). The reliability of the cut-off values was validated using bootstrap resampling ($n = 1000$),[13] and 95% confidence intervals (95% CIs) based on bootstrap percentiles were presented. The statistical software package R (version 2.5.1) was used for bootstrap analysis. For QTc, we used the established cut-off value of 0.46 s.[14] For the area under the ROC curve, 95% CIs were presented. Reproducibility was expressed as intraclass correlation coefficient for single measures. For all statistical analyses, *P*-values were two-sided, with results less than 0.05 considered significant.

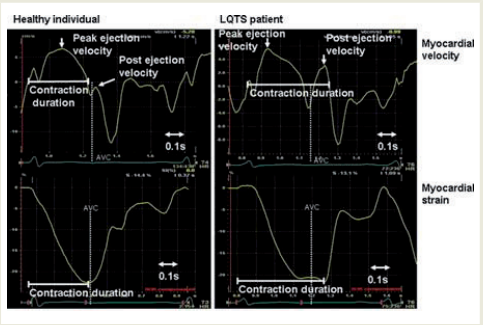

Figure 2 Myocardial contraction duration by tissue Doppler imaging. Myocardial velocities (upper panels) and strains (lower panels) from a healthy individual (left) and a long QT syndrome patient (right).

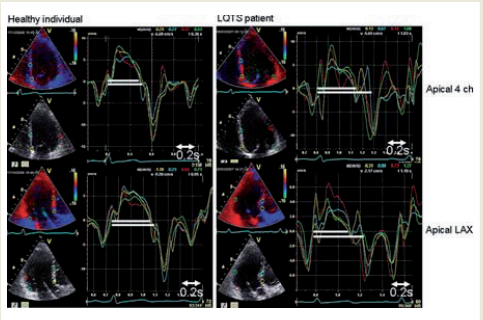

Figure 3 Myocardial mechanical dispersion by tissue Doppler imaging. The left panels show velocity curves from four different segments in a healthy individual in four-chamber (upper left) and apical long-axis views (lower left). The right panels show velocity curves from a symptomatic long QT syndrome patient. White markers show the shortest and the longest contraction durations in each person. The difference in contraction duration is 0.03 s in the healthy individual and 0.12 s in the long QT syndrome patient and is consistent with the mechanical dispersion of contraction.

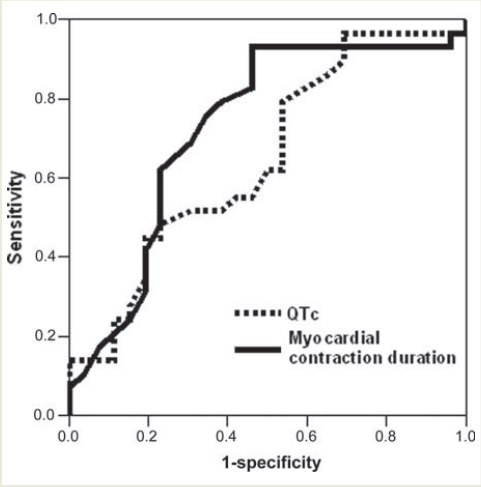

Figure 4 Receiver-operating characteristic curves of cardiac events (documented arrhythmia, syncope, or aborted cardiac arrest) in 64 single long QT syndrome mutation carriers (33 symptomatic and 31 asymptomatic). Myocardial contraction duration shows higher sensitivity and specificity for cardiac events compared with corrected QT interval. Area under curve 0.77 (95% CI 0.65–0.89) vs. 0.66 (95% CI 0.52–0.79).

Results

All groups of LQTS mutation carriers were comparable with healthy individuals with respect to age and heart rate (*Table 1*). The QTc was prolonged in each of the LQTS groups compared with the control groups. EF and peak ejection velocity, as markers of systolic function, were normal in all LQTS groups, in healthy individuals and in individuals on beta-blocker therapy (*Table 1*).

Echocardiographic analysis by tissue Doppler imaging

Contraction duration was assessed in both myocardial velocity and strain traces with consistent results.

Long QT syndrome single-mutation carriers

Contraction duration was significantly longer in symptomatic LQTS single-mutation carriers compared with asymptomatic carriers and healthy individuals ($P = 0.001$) (*Table 1*). In contrast to healthy individuals, LQTS mutation carriers showed contraction durations that exceeded the time to aortic valve closure. Patients on beta-blocker therapy did not have prolonged contraction duration. Therefore, the prolonged contraction duration in LQTS mutation carriers could not be attributed to the use of beta-blocker medication. Mechanical dispersion, assessed as standard deviation of contraction duration, was significantly greater in LQTS single-mutation carriers compared with healthy individuals ($P < 0.001$) and compared with individuals on beta-blocker therapy ($P < 0.001$). In addition, mechanical dispersion was significantly greater in symptomatic compared with asymptomatic single-mutation carriers ($P = 0.001$). The correlation between contraction duration and QTc was significant ($R = 0.43$, $P < 0.001$).

A marked PEV was observed in LQTS mutation carriers and was significantly greater than PEV found in healthy individuals (*Figure 2*, *Table 1*). In addition, the maximum PEV in symptomatic LQTS single-mutation carriers was greater than that in asymptomatic LQTS mutation carriers ($P = 0.001$). The maximum PEV was most often localized in the posterior part of the LV septum ($n = 34$), but was also found in the anterior part of the septum ($n = 17$), in the anterior wall ($n = 12$), in the lateral wall ($n = 9$), and in the posterior wall ($n = 1$) of the LV.

The onset of the E′ was delayed in symptomatic LQTS single-mutation carriers compared with asymptomatic mutation carriers and control subjects. Age-corrected E′-wave velocities were lower in symptomatic than in asymptomatic mutation carriers [7.9 ± 1.9 vs. 8.9 ± 1.9 cm/s; $P = 0.02$ (Univariate Analysis of Variance)].

Subgroup analysis of LQT1 and LQT2 patients (data not presented) did not show significant differences in the echocardiographic parameters.

We wanted to explore the incremental value provided by echocardiography in LQTS mutation carriers. JLNS patients (double mutation) were considered a separate category and not necessarily representative of the more common patients with a single mutation. Therefore, we constructed ROC curves for LQTS single-mutation carriers exclusively ($n = 64$). By ROC analysis, contraction duration identified single-mutation carriers with a history of cardiac events with better specificity and sensitivity than QTc did (*Figure 4*). QTc $\geq$0.46 s showed a sensitivity of 70% (95% CI 67–88) and a specificity of 50% (95% CI 40–61) to identify single-mutation carriers with a history of events. Contraction duration identified single-mutation carriers with a history of events with a sensitivity of 79% (95% CI 68–87) and a specificity of 74% (95% CI 62–83) with an optimal cut off value of 0.44 s (95% CI by bootstrapping 0.41–0.46). Importantly, contraction duration was prolonged in all six symptomatic single-mutation carriers that exhibited QTc shorter than 0.46 s. Optimal cut-off value for PEV was 1.65 cm/s (95% CI by bootstrapping 1.24–2.23) and demonstrated a sensitivity of 70% (95% CI 58–79) and a specificity of 68% (95% CI 55–78) for a history of cardiac events in single-mutation carriers by ROC analysis.

Long QT syndrome double-mutation carriers

QTc was markedly prolonged in double-mutation carriers compared with all other groups ($P < 0.001$) (*Table 1*). Contraction duration was prolonged and PEV augmented compared with healthy individuals and asymptomatic single-mutation carriers. Mechanical dispersion was longer than in healthy individuals, but not significantly different from single-mutation carriers.

The intra- and interobserver variabilities of PEV measurements demonstrated an intraclass correlation coefficient of 0.92 (95% CI 0.84–0.96) and 0.79 (95% CI 0.68–0.86), respectively, and for contraction duration measurements of 0.97 (95% CI 0.92–0.99) and 0.92 (95% CI 0.72–0.98), respectively.

Table I Clinical characteristics and echocardiographic results

	Healthy individuals ($n = 20$)	LQTS single-mutation carrier asymptomatic ($n = 31$)	LQTS single-mutation carrier symptomatic ($n = 33$)	LQTS double-mutation (JLNS) carrier symptomatic ($n = 9$)	Individuals on beta-blocker medication ($n = 18$)	*P*-value (ANOVA *F*-test)
Clinical characteristics						
Age (years)	34 ± 11	41 ± 14	33 ± 15	27 ± 21	59 ± 10	0.04
Women [*n* (%)]	11 (55)	21 (68)	25 (76)	8 (89)	10 (56)	
RR (s)	0.90 ± 0.16	0.93 ± 0.17	0.99 ± 0.19	0.94 ± 0.23	0.93 ± 0.19	0.47
QTc	0.39 ± 0.02	0.46 ± 0.03*	0.48 ± 0.04*	0.56 ± 0.05**	0.41 ± 0.03	<0.001
Echocardiographic results						
EF (%)	67 ± 3	64 ± 6	64 ± 6	63 ± 5	66 ± 5	0.59
CD by velocity (s)	0.36 ± 0.04	0.40 ± 0.06*	0.46 ± 0.06*, ***	0.48 ± 0.06*, ***	0.38 ± 0.04	<0.001
CD by strain (s)	0.39 ± 0.03	0.45 ± 0.05*	0.49 ± 0.05*, ***	0.50 ± 0.07*, ***	0.40 ± 0.03	<0.001
Standard deviation of CD by velocity (s)	0.014 ± 0.013	0.031 ± 0.019*	0.048 ± 0.018*, ***	0.036 ± 0.021*	0.024 ± 0.016	<0.001
Time to aortic valve closure (s)	0.36 ± 0.01	0.39 ± 0.03*	0.40 ± 0.03*	0.42 ± 0.05*	0.40 ± 0.03	<0.001
Peak ejection velocity (cm/s)	6.2 ± 1.0	6.1 ± 1.1	5.9 ± 0.8	5.5 ± 0.9	5.5 ± 0.9	0.27
PEV (cm/s)	−0.2 ± 0.7	1.1 ± 1.3*	2.3 ± 1.3*, ***	2.5 ± 1.3*, ***	0.0 ± 0.8	<0.001
Onset E′ wave (s)	0.40 ± 0.03	0.44 ± 0.04*	0.47 ± 0.05*	0.48 ± 0.07*	0.46 ± 0.04	<0.001
E′ (cm/s)	9.8 ± 2.3	8.8 ± 2.0	7.9 ± 2.0*	7.8 ± 2.3	9.8 ± 2.7	0.02
E deceleration time (s)	0.15 ± 0.01	0.19 ± 0.03	0.19 ± 0.04	0.23 ± 0.08*	0.20 ± 0.04	0.10

Mean ± SD. Right column shows *P*-values for ANOVA test. Flags for significance are obtained from the *post hoc* pair-wise comparison using the Bonferroni correction.
Results from individuals on beta-blocker medication are not included in the ANOVA analyses.
CD, contraction duration.
*$P < 0.05$ compared with healthy individuals.
**$P < 0.001$ compared with each of the other groups.
***$P < 0.05$ compared with asymptomatic LQTS single-mutation carriers.

Discussion

The present study demonstrated that analyses of tissue Doppler velocities added important information in patients with LQTS. Prolonged contraction duration showed better specificity and sensitivity than QTc as a marker of cardiac events and therefore provided added value in risk assessment in LQTS mutation carriers. The contraction duration showed greater heterogeneity in LQTS mutation carriers than in controls, reflecting dispersion of myocardial contraction, presumably caused by electrical dispersion of repolarization. LQTS mutation carriers showed a marked increase in PEV, indicating myocardial shortening after aortic valve closure. These findings were associated with a history of cardiac events.

Possible mechanisms

In the normal heart, several mechanisms regulate myocyte repolarization. As the QT interval on the surface ECG represents the summation of action potentials in ventricular myocytes, QT prolongation implies action potential prolongation in at least some portions of the ventricle. A prolongation of the action potential duration is associated with an increase in the tension developed by the ventricular muscle, leading to a prolonged contraction.[6–8] In this study, the prolonged contraction in LQTS mutation carriers was assessed by TDI.

Action potential prolongation can lead to the development of early EADs, which are oscillations in the membrane potential before repolarization is complete. EADs may result in a second contraction and lead to ectopic beats if occurring in a substantial part of the myocardium.[15] Triggered upstrokes from EADs are a likely initiating mechanism for torsade de pointes ventricular tachycardia.[16–18] The prolonged contraction duration and the augmented PEV in LQTS mutation carriers could represent the mechanical equivalent of an electrical EAD as proposed by De Ferrari *et al.*[10] This is consistent with the finding that symptomatic LQTS mutation carriers had greater PEV than asymptomatic mutation carriers. EADs may be present at subthreshold levels in LQTS mutation carriers also in basal conditions, without leading to arrhythmias but causing contraction prolongation and PEV.

In the majority of our LQTS mutation carriers, we found the greatest magnitude of the PEV in basal and mid-LV septal regions. Previous reports have demonstrated that action potentials of the mid-myocardial cells (M-cells) prolong more than epicardial or endocardial in response to a lowering of heart rate or to action potential-prolonging agents.[19] A prolonged action potential leads to a higher risk of EAD.[15] M-cells have been identified in the interventricular septum and in the anterior and lateral walls.[20] The localization of the reported M-cells matched the regions of the greatest PEV in our LQTS patients. Therefore, we speculated that PEV and prolonged contraction assessed by TDI could be a result of the prolonged action potentials in these M-cells that are known to have the longest action potential duration.

A possible mechanism of arrhythmia in LQTS patients is increased dispersion of repolarization.[21] Dispersion of repolarization may be localized between two different ventricular regions and as a transmural phenomenon.[22,23] The measurement of QTc and QT dispersion as indicators of ventricular repolarization prolongation and dispersion have been widely used during the last two decades.[24] However, identification of the end of the T-wave is difficult and measurements of dispersion by ECG have modest reproducibility.[25] The TDI method has the ability to measure detailed time intervals in different regions of the LV. Our study clearly demonstrated that the dispersion of mechanical contraction can be assessed by TDI, as a regional difference in contraction duration throughout the LV. Furthermore, that mechanical dispersion was more pronounced in symptomatic compared with asymptomatic LQTS patients.

Double-mutation carriers, JLNS patients, represent the most severe clinical phenotype and were therefore analysed separately in this study. The presence of two mutations (JLNS) is associated with higher risk of cardiac events and more widespread current loss.[26] In our study, these facts were supported by a more prolonged contraction duration in a greater number of cardiac segments in JLNS patients compared with single-mutation carriers. Standard deviation of contraction duration was therefore lower in the JLNS patients. Pronounced prolongation of contraction duration may indicate that EADs are the most likely mechanism for arrhythmia in JLNS patients.

The contraction duration in LQTS mutation carriers exceeded the time to aortic valve closure. This indicated myocardial contraction after aortic valve closure, which may be a result of an inhomogeneous end of contraction not sufficient to maintain the opening of the aortic valve. If the dispersion of contraction reflects the electrical dispersion of repolarization, a major arrhythmogenic factor present in LQTS mutation carriers can be shown by echocardiography.

A prolonged myocardial contraction will lead to inhomogeneous and delayed onset of the E′ wave. Furthermore, an inhomogeneous onset of diastolic lengthening will cause reduced E′ amplitude and prolonged duration of E′. These assumptions were confirmed in our study that showed delayed onset of E′, reduced amplitude of the E′, and prolonged E deceleration time. These findings imply an impairment of diastolic function in a number of symptomatic LQTS mutation carriers.

Previous studies

Echocardiography has traditionally been used to exclude structural heart disease in LQTS patients. However, Nador *et al.* presented an echocardiographic study which showed specific ventricular wall abnormalities in 42 LQTS patients.[9] Using M-mode technique, they demonstrated the occurrence of a slow contraction in the late myocardial thickening phase. Further they demonstrated a dip in the later part of contraction followed by a second anterior movement of the endocardium producing a double-peak image. Interestingly, their findings were associated with a greater probability of syncope or cardiac arrest. These findings are confirmed in our study. We showed that prolonged contraction duration and increased PEV, which give a similar double-peak pattern, are associated with cardiac events. Another study has shown mechanical abnormality by M-mode technique in LQTS patients.[27] Their findings were attributed to mechanical dispersion possibly caused by electrical dispersion of repolarization. A recent case report indicated mechanical dysfunction in a patient with extreme QT prolongation.[28] A recent study showed myocardial velocity

abnormalities in 10 LQTS patients.[29] Our study confirms these findings using a new modality of echocardiography. We believe that TDI measurements may be an easier and more objective way of quantifying abnormal regional motion than M-mode echocardiography. The study by Nador *et al.* was followed by a study giving calcium channel blockers to 10 LQTS patients.[10] Verapamil abolished the wall motion abnormality, suggesting that symptomatic LQTS patients may have an abnormal increase in the intracellular calcium concentration before relaxation has completed, possibly linked to an EAD, and that the contraction abnormality may be the mechanical equivalent of an EAD.

Post-systolic shortening after aortic valve closure, which is similar but not identical to PEV, has been demonstrated in ischaemic myocardium[30,31] and may also occur in healthy individuals.[32] PEV in ischaemic heart disease is of greater magnitude compared with PEV in healthy individuals, and a coexisting reduction in ejection velocity is obligate.[32] PEV can even be negative if post-systolic shortening is missing in healthy individuals.[32,33] The LQTS mutation carriers had normal systolic ejection velocities and ejection fraction. Thus, the elevated PEV in LQTS mutation carriers was not considered to be a result of earlier cardiac arrests with concomitant myocardial ischaemia.

Clinical implications

QTc is the most rational parameter for screening patients with unexplained syncope or cardiac arrest. In known LQTS patients, risk stratification is based on the occurrence of previous syncope, genotype, gender, and QTc.[1] The recent development from family cascade genetic screening has brought us numerous LQTS mutation carriers with normal QTc, who would have been undiagnosed before the genetic era. These asymptomatic mutation carriers demonstrate neither clinical symptoms nor prolonged QTc. Nevertheless, they have increased risk of ventricular arrhythmia and sudden cardiac death. It is a clinical challenge to decide whether these asymptomatic mutation carriers should receive prophylactic treatment or not. Assessment of myocardial contraction duration may add important information in risk stratification in LQTS mutation carriers when QTc is normal or mildly prolonged. Our data showed that myocardial contraction duration had higher sensitivity and specificity for a history of cardiac events than QTc. Importantly, in all symptomatic mutations carriers that QTc failed to identify, contraction duration by echocardiography was prolonged ($\geq$0.44 s).

Our study did not provide data that actually demonstrated that asymptomatic LQTS mutation carriers with prolonged contraction duration and elevated PEV were more likely to develop arrhythmias than those without. This requires a prospective study in which asymptomatic untreated patients are followed for an adequate period of time, which is difficult for ethical reasons. Nevertheless, we propose that TDI should become part of the routine clinical evaluation for LQTS mutation carriers. The myocardial contraction duration is relatively simple to obtain and has excellent reproducibility for inter and intra-observations.

Limitations

Prolonged contraction duration by strain in this study was highly significant as a risk parameter for cardiac events. However, the results assessed by myocardial velocities were significantly associated with cardiac events and therefore we preferred velocity to strain measurements since the reproducibility of this method is superior.[34] Circumferential and radial strains were not analysed in this study.

A limitation of TDI is marked angle dependency, which makes it sensitive to mal-alignment between the principal direction of myocardial shortening and the Doppler beam. Owing to less angle dependency, time interval assessment provided by TDI is a better reproducible parameter than measurements of velocity amplitudes.

The association between myocardial mechanical and electrical dispersion in LQTS mutation carriers should be studied in experimental studies.

Conclusion

This study showed that TDI can be of important value in risk stratification of LQTS mutation carriers. Mechanical dispersion of myocardial contraction assessed by TDI was increased in LQTS patients. Prolonged myocardial contraction duration and augmented PEV were better related to cardiac events compared with QTc. Therefore, we propose that these novel parameters might be assessed in the management of LQTS patients.

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II

Transmural Differences in Myocardial Contraction in Long-QT Syndrome

Mechanical Consequences of Ion Channel Dysfunction

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Background—Long-QT syndrome (LQTS) is characterized by prolonged myocardial action potential duration. The longest action potential duration is reported in the endomyocardium and midmyocardium. Prolonged action potential duration in LQTS may cause prolonged cardiac contraction, which can be assessed by strain echocardiography. We hypothesized that myocardial contraction is most prolonged in subendocardial myofibers in LQTS patients and that inhomogeneous transmural contraction is related to the risk of spontaneous arrhythmia.

Methods and Results—We included 101 genotyped LQTS mutation carriers and 35 healthy individuals. A history of cardiac arrhythmias was present in 48 mutations carriers, and 53 were asymptomatic. Myocardial contraction duration was assessed by strain echocardiography as time from the ECG Q wave to peak strain in 16 LV segments. Strain was assessed along the longitudinal axis, predominantly representing subendocardial fibers, and along the circumferential axis, representing midmyocardial fibers. Mean contraction duration was longer in LQTS mutation carriers compared with healthy individuals (445±45 versus 390±40 milliseconds; $P<0.001$) and longer in symptomatic compared with asymptomatic LQTS mutation carriers (460±40 versus 425±45 milliseconds; $P<0.001$). Contraction duration by longitudinal strain was longer than by circumferential strain in symptomatic LQTS patients (460±45 versus 445±45 milliseconds; $P=0.008$) but not in asymptomatic patients and healthy individuals, indicating transmural mechanical dispersion. This time difference was present in a majority of LV segments and was most evident in patients with LQT2 and the Jervell and Lange-Nielsen syndrome.

Conclusion—Contraction duration in symptomatic LQTS mutation carriers was longer in the subendocardium than in the midmyocardium, indicating transmural mechanical dispersion, which was not present in asymptomatic and healthy individuals. **(*Circulation*. 2010;122:1355-1363.)**

Key Words: echocardiography ■ long QT syndrome ■ torsade de pointes ■ transthoracic echocardiography ■ arrhythmia

The long-QT syndrome (LQTS) is due to inherited cardiac ion channel defects and predisposes to life-threatening ventricular arrhythmias and sudden cardiac death. Its prevalence has been estimated as 1 in 2000.[1] LQTS-related ion channels defects lead to prolonged cardiac action potential duration (APD). The degree of action potential prolongation and dispersion in timing of action potential repolarization have been considered the major mechanisms behind the ventricular arrhythmias in these patients. Earlier invasive studies have indicated that the duration of the cardiac action potential is not homogeneous throughout the myocardium in either normal or genetically altered myocardial tissue.[2,3] The longest APD in LQTS models has been reported in endocardial Purkinje cells and in subendocardial to midmyocardial cells (M cells).[4,5] Transmural differences in APD have been considered to be of major importance in arrhythmogenesis in LQTS patients.[6] However, it has been challenging to assess APD and dispersion in patients. Attempts to estimate action potential dispersion in terms of QT dispersion have not been clinically useful.[7]

Editorial see p 1353
Clinical Perspective on p 1363

Left ventricular (LV) function has been considered normal in LQTS patients. There is, however, support for the assumption that subtle electric changes may cause mechanical dysfunction. Nador et al[8] and De Ferrari et al[9] have reported wall motion abnormalities in LQTS patients. We recently

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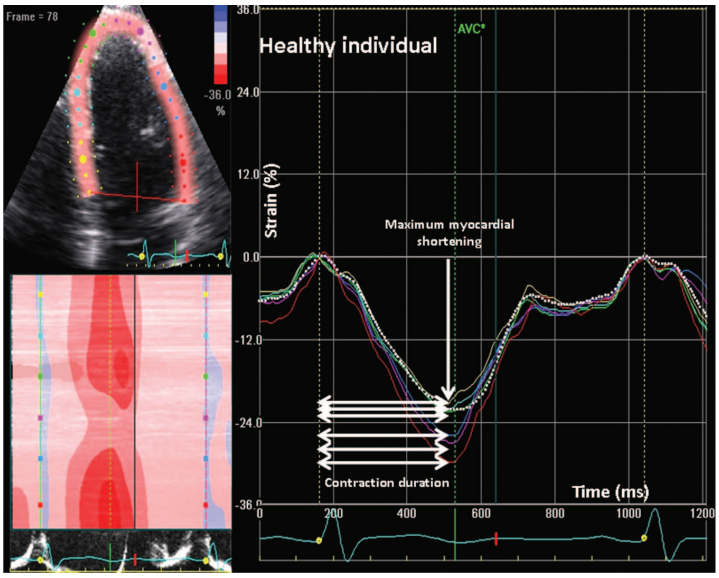

Figure 1. Longitudinal myocardial strain curves from a healthy individual in the apical 4-chamber view. Vertical arrow indicates the amplitude of maximum myocardial shortening in the septal basal segment (yellow strain curve). Contraction duration was defined as the time from the Q wave or start of the R wave on the ECG to maximum myocardial shortening of each strain curve (horizontal arrows). The SD of contraction durations from 16 LV segments was calculated as mechanical dispersion. AVC indicates aortic valve closure.

reported prolonged myocardial contraction duration and pronounced mechanical dispersion assessed by echocardiographic velocity measurements in patients with LQTS,[10] and these mechanical abnormalities were associated with a higher risk of cardiac arrhythmias. These results supported that the electric mechanisms for arrhythmia in LQTS may be translated into mechanical contraction abnormalities, including prolongation and dispersion of myocardial contraction duration.

Myocardial strain measurements have been proven to be superior for assessment of regional LV function.[11,12] The subendocardium consists mainly of longitudinal myocardial fibers, whereas the midmyocardium consists mainly of circumferentially oriented fibers.[13] As a result of this myocardial fiber geometry, strain measurements are able to indirectly discriminate between transmural contraction differences (ie, differences between subendocardial and midmyocardial layers).

We hypothesized that myocardial contraction is inhomogeneously prolonged throughout the LV in LQTS patients and that the longest contraction duration is located in the subendocardium where the longest APD has been reported. Furthermore, we wanted to investigate whether the heterogeneity of prolonged contraction is related to specific genotypes and the risk for spontaneous arrhythmia in LQTS patients.

Methods

LQTS Mutation Carriers

A total of 101 genotyped LQTS mutation carriers were included in this study. Sixty-four patients were heterozygous for a mutation in the LQT1 locus and 26 in the LQT2 locus. Only 1 patient was heterozygous for a mutation in the LQT3 locus and 1 in the LQT5 locus. A relatively high proportion of the study patients (n=9) were homozygotes or compound heterozygotes for mutations in the LQT1 locus (Jervell and Lange Nielsen syndrome [JLNS]). In all, 48 (48%) had a history of documented arrhythmia, syncope, or cardiac arrest, defined here as symptomatic, and 53 (52%) were asymptomatic mutation carriers who were recruited from family cascade genetic screening. β-Blocker medications at the time of the examination used in the study were metoprolol succinate in 37 patients (113±47 mg/d), timolol in 7 patients (15±3 mg/d), propranolol in 6 patients (188±106 mg/d), and bisoprolol (10±0 mg/d) in 2 patients. In addition to β-blocker therapy, 6 mutation carriers were treated with an implantable cardioverter-defibrillator and 3 with an atrial pacemaker. One JLNS patient was also treated with left sympathetic denervation. None of the LQTS patients had structural heart disease of other origin. We did not include asymptomatic mutation carriers <18 years of age because we regarded them as too young to be classified as truly asymptomatic.

Control Group

Healthy individuals from the hospital staff (n=35) with age and sex corresponding to the patients were recruited as a control group for the echocardiographic measurements. ECG, heart rate correction of the QT interval (QTc), and echocardiography showed normal findings in all healthy individuals.

Written informed consent was given by all study participants. The study was approved by the Regional Committee for Medical Research Ethics.

Electrocardiography

Twelve-lead ECG was obtained at the time of echocardiographic examination. The Bazett formula was used for QTc.[14] QTc dispersion was measured as the difference between longest and shortest QTc intervals in any of the 12 ECG leads.[15,16]

Echocardiographic Studies

The echocardiographic studies were performed on a Vivid 7 (GE Healthcare, Horten, Norway). Data were analyzed with EchoPAC (GE Healthcare). LV ejection fraction was assessed with the Simpson method from 2-dimensional echocardiography.

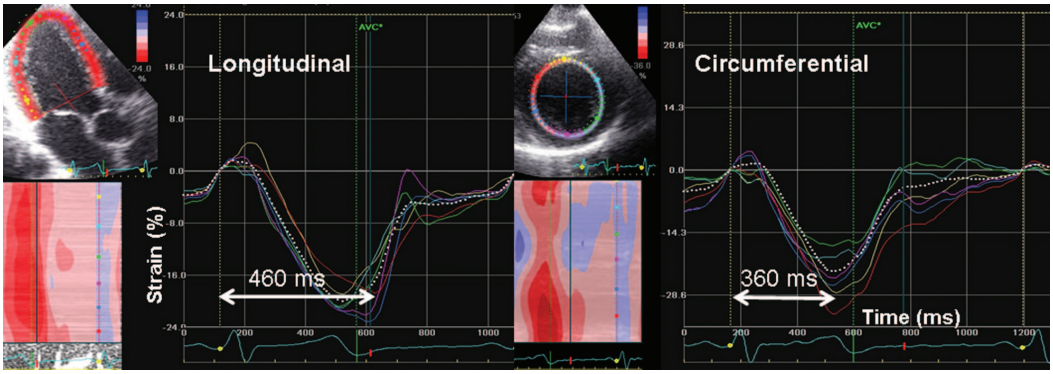

Figure 2. Transmural mechanical dispersion in a symptomatic LQTS patient. Shown are the longitudinal (left) and circumferential (right) strain curves from a symptomatic LQTS patient. The anterior basal septal segment from longitudinal strain (left, red curve) shows a contraction duration of 460 milliseconds. From circumferential strain, the contraction duration from the anterior basal septal segment (right, yellow curve) is 360 milliseconds. Subendocardial contraction duration (longitudinal strain) therefore is markedly prolonged compared with midmyocardial contraction duration (circumferential strain), indicating transmural mechanical dispersion.

Myocardial Strain Measurements

We assessed longitudinal and circumferential strains by the speckle tracking technique[17] with a frame rate of 76±18 frames per second. Three cardiac cycles were analyzed.

We assessed the following parameters from myocardial strain: maximum myocardial shortening (Figure 1); global strain calculated as the average of longitudinal maximum myocardial shortening from 16 LV segments; time from ECG onset of the Q wave (onset of the R wave if the Q wave was absent) to maximum myocardial shortening defined as contraction duration (Figure 1); SD of the 16 longitudinally measured and 6 circumferentially measured contraction durations calculated as parameters of mechanical dispersion; time difference between the longest and shortest contraction durations defined as delta contraction duration in the longitudinal and circumferential directions; and transmural mechanical dispersion expressed by the time difference in longitudinal and circumferential contraction durations of the 6 basal LV segments (Figure 2).

Because tissue Doppler imaging (TDI) had higher temporal resolution (129±28 frames per second) compared with speckle tracking measurements, TDI recordings of the LV were obtained from the apical 4-chamber, 2-chamber, and long-axis views as previously described.[10]

Heart rate was recorded at time of echocardiographic examination, and all echocardiographic time measurements were corrected for heart rate with the Bazett formula.[14] Myocardial strain could be assessed in 98% of the myocardial segments in LQTS mutation carriers and in 94% of the segments in the healthy individuals. The primary analysis was done by a single observer and repeated in a blinded fashion. For contraction duration, intraobserver, interobserver, and test-retest intraclass correlations were 0.96, 0.96, and 0.87, respectively; for mechanical dispersion, they were 0.98, 0.89, and 0.79, respectively. The corresponding QTc and QTc dispersion test-retest intraclass correlations were 0.82 and 0.67, respectively.

Statistical Analyses

Continuous data are presented as mean±SD or as median (range). Comparisons of means between groups of patients were performed by unpaired Student *t* test (SPSS 15.0, SPSS Inc, Chicago, Ill). The paired *t* test was used for all comparisons within the same patient. Comparisons of proportions were performed by the Fisher exact test. Receiver-operating characteristic (ROC) curves were created for longitudinal mechanical dispersion and QTc to determine the discrimination of these parameters, ie, the ability to distinguish between LQTS mutation carriers with and without cardiac events (documented arrhythmia, syncope, or cardiac arrest). The optimal cutoff value for mechanical dispersion was defined as the value from the ROC curve closest to the top left corner. The sensitivity and specificity for the optimal cutoff value were reported. For QTc, the established cutoff value of 460 milliseconds was used.[18] The area under the ROC curve (AUC) was calculated for both parameters, and comparison between AUCs[19] was performed with the Analyze-it software. For all statistical analyses, *P* values were 2 sided. Values of $P<0.05$ were considered statistically significant.

Results

Myocardial Function in LQTS Patients

Clinical characteristics and echocardiographic data are presented in Table 1. Age and heart rate were similar in LQTS

Table 1. Clinical Characteristics and Echocardiographic Findings in 101 LQTS Mutation Carriers and 35 Healthy Individuals

	Healthy Individuals (n=35)	LQTS Patients (n=101)	*P*
Age, y	34±10	37±16	0.32
Heart rate, bpm	69±10	65±13	0.27
Women, n (%)	20 (57)	71 (70)	0.21
EF, %	64±5	64±6	0.83
Global strain, %	−22.6±2.0	−21.4±1.8	0.009
Mean contraction duration, longitudinal, ms	390±40	445±45	<0.001
Mean contraction duration, circumferential, ms	385±45	430±50	<0.001
Mechanical dispersion, longitudinal, ms	20±7	36±15	<0.001
Mechanical dispersion, circumferential, ms	14±11	36±23	<0.001
Delta contraction duration, longitudinal, ms	55±20	110±50	<0.001
Delta contraction duration, circumferential, ms	25±25	88±55	<0.001

EF indicates ejection fraction. Values are mean±SD when appropriate. *P* values are from unpaired *t* test and Fisher exact test.

patients and healthy individuals. Ejection fraction was normal in LQTS subjects regardless of previous arrhythmias. LQTS patients had longer QTc compared with healthy individuals (480±45 versus 390±20 milliseconds; $P<0.001$). Despite apparently normal systolic LV function, mean contraction duration was significantly longer in LQTS patients compared with healthy individuals in longitudinal and circumferential measurements (both $P<0.001$). The abnormal myocardial function in LQTS mutation carriers was further confirmed by a significantly more pronounced mechanical dispersion (heterogeneous contraction) compared with healthy individuals ($P<0.001$). Finally, delta contraction duration, reflecting the difference between the longest and shortest contraction durations, was prolonged in LQTS patients ($P<0.001$). Global strain as a marker of systolic function was within normal range in LQTS patients but was significantly reduced compared with healthy individuals ($P=0.009$).

Results in Symptomatic Compared With Asymptomatic LQTS Mutation Carriers and Arrhythmia Risk Evaluation

Symptomatic LQTS mutation carriers had longer QTc ($P<0.001$) and pronounced QTc dispersion ($P=0.04$) compared with asymptomatic mutation carriers (Table 2). Mean contraction duration was longer in symptomatic LQTS mutation carriers compared with asymptomatic carriers in longitudinal ($P<0.001$) and circumferential ($P=0.03$) measurements. In symptomatic LQTS patients, mean contraction duration measured by longitudinal strain was significantly longer compared with circumferential strain (460±45 versus 445±45 milliseconds; $P=0.008$), reflecting transmural mechanical dispersion. Significant differences between subendocardial and midmyocardial contraction durations were present in the following segments in symptomatic LQTS mutation carriers: posterior septal: 465±60 milliseconds for longitudinal versus 415±50 milliseconds for circumferential, $P<0.001$; anterior septal: 470±65 milliseconds for longitudinal versus 440±60 milliseconds for circumferential, $P=0.04$; anterior segment: 485±65 milliseconds for longitudinal versus 445±65 milliseconds for circumferential, $P=0.02$; posterolateral segment: 480±50 milliseconds for longitudinal versus 425±65 milliseconds for circumferential, $P=0.01$; and posterior segment: 480±65 milliseconds for longitudinal versus 440±65 milliseconds for circumferential, $P=0.003$. In asymptomatic LQTS mutation carriers and healthy individuals, there were no significant differences in mean contraction duration measured by longitudinal compared with circumferential strain ($P=0.31$ and $P=0.99$, respectively), indicating an absence of transmural mechanical dispersion.

Mechanical dispersion, assessed as the SD of contraction duration, was significantly greater in symptomatic LQTS mutation carriers compared with asymptomatic patients in both strain directions ($P<0.001$; Table 2 and Figure 3). The time differences between the longest and the shortest contraction durations longitudinally and circumferentially (delta contraction durations) were significantly longer in symptomatic LQTS mutation carriers ($P<0.001$). As determined by ROC analysis, longitudinal mechanical dispersion could better discriminate between LQTS mutation carriers with and without cardiac events compared with QTc with an AUC of 0.87 (95% confidence interval [CI], 0.79 to 0.94; Figure 4). The AUC for mechanical dispersion was significantly higher compared with the AUC for QTc (AUC, 0.71; 95% CI, 0.61 to 0.81; $P<0.01$). QTc ≥460 milliseconds showed a sensitivity of 42% (95% CI, 29 to 57) and a specificity of 81% (95% CI, 67 to 91) for identifying mutation carriers with a history of events. The optimal cutoff value for mechanical dispersion was ≥33 milliseconds and identified mutation carriers with a history of events with a sensitivity of 76% (95% CI, 61 to 87) and a specificity of 91% (95% CI, 78 to 98). There was a modest but significant correlation between QTc dispersion by ECG and mechanical dispersion by echocardiography ($r=0.30$, $P=0.007$).

The echocardiographic study was repeated in 10 patients after a median of 16 months (range, 6 to 38 months). No changes in medication were initiated in these patients between the 2 echocardiographic studies. Contraction duration and mechanical dispersion did not change significantly over time. Contraction durations at the first and second echocardiographic studies were 465±65 and 435±30 milliseconds, respectively ($P=0.12$). Mechanical

Table 2. Clinical Characteristics and Echocardiographic Findings in 53 Asymptomatic and 48 Symptomatic LQTS Mutation Carriers

	Asymptomatic LQTS Patients (n=53)	Symptomatic LQTS Patients (n=48)	*P*
Age, y	41±14	32±16	0.002
Heart rate, bpm	67±13	64±13	0.22
Women, n (%)	32 (60)	39 (81)	0.03
EF, %	64±6	64±5	0.50
Global strain, %	−21.2±1.6	−21.5±1.9	0.41
QTc, ms	460±30	495±50	<0.001
QTc dispersion, ms	48±17	56±23	0.04
LQT1, n (%)	40 (75)	24 (50)	0.005
LQT2, n (%)	12 (23)	14 (29)	0.81
LQT3, n (%)	1 (2)	0 (0)	0.99
LQT5, n (%)	0 (0)	1 (2)	0.48
JLNS, n (%)	0 (0)	9 (100)	0.001
Mean contraction duration, longitudinal, ms	425±45	460±40	<0.001
Mean contraction duration, circumferential, ms	415±55	440±45	0.03
Mechanical dispersion, longitudinal, ms	27±12	45±13	<0.001
Mechanical dispersion, circumferential, ms	26±21	46±22	<0.001
Delta contraction duration, longitudinal, ms	85±40	130±50	<0.001
Delta contraction duration, circumferential, ms	55±50	100±55	<0.001

EF indicates ejection fraction. Values are mean±SD when appropriate. *P* values are from unpaired *t* test and Fisher exact test.

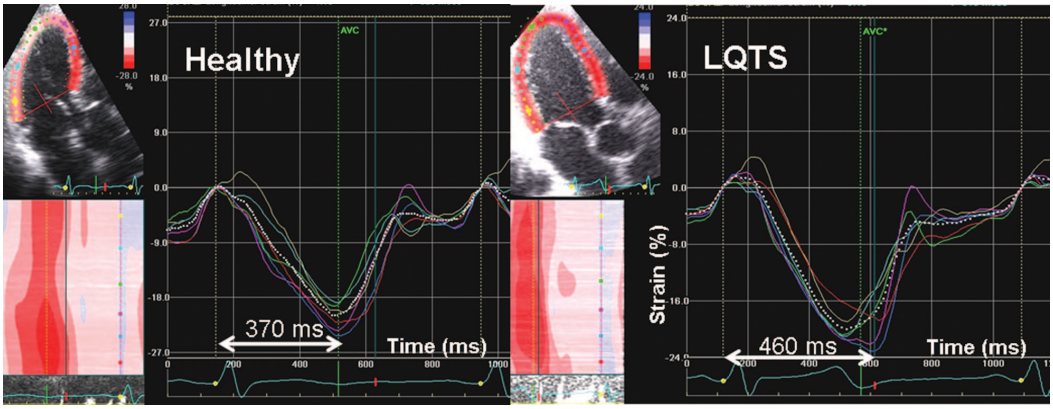

Figure 3. Myocardial strain curves from the apical long-axis view in a healthy individual (left) and an LQTS patient (right). Contraction duration is homogeneous in all 6 segments in the healthy individual (370 milliseconds). The LQTS patient shows prolonged contraction duration (460 milliseconds) in the 3 septal segments (red, dark blue, and pink strain curves), indicating dispersed myocardial contraction. AVC indicates aortic valve closure.

dispersions at the same occasions were 43±19 and 37±10 milliseconds (P=0.17).

All longitudinal time measurements were repeated by the TDI method because of the higher temporal resolution. These time measurements showed results similar to those of speckle tracking (data not presented). The intraclass correlation between contraction duration by TDI and the speckle tracking technique was 0.84.

β-Blocker therapy was more common in symptomatic LQTS mutation carriers (85%) compared with asymptomatic carriers (21%; P<0.001). However, heart rate at the time of echocardiographic examination was not significantly different in the 2 groups (Table 2).

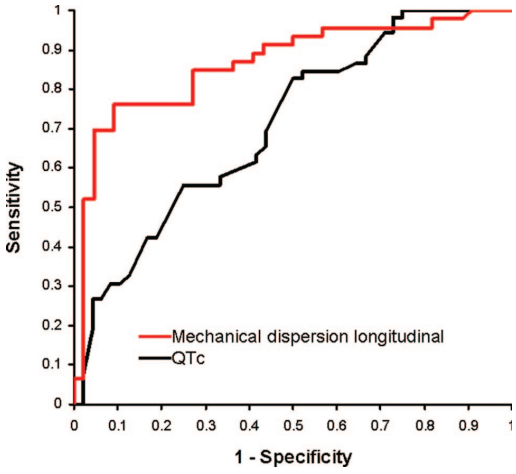

Figure 4. ROC curves of cardiac events in 101 LQTS mutation carriers. Mechanical dispersion demonstrates better discrimination of patients who experience cardiac events compared with QTc. AUC for mechanical dispersion is 0.87 (95% CI, 0.79 to 0.94) versus 0.71 for QTc (95% CI, 0.61 to 0.81; P<0.01).

Genotype Subgroup Analyses

Subgroup analyses of LQT1 (n=64) and LQT2 (n=26) single-mutation carriers did not show significant differences in QTc (470±35 versus 470±30 milliseconds; P=0.85) or mean contraction duration longitudinally (435±45 versus 445±50 milliseconds; P=0.50) or circumferentially (430±55 versus 420±45 milliseconds; P=0.40). Longitudinal mechanical dispersion tended to be more pronounced in LQT2 compared with LQT1 patients (37±14 versus 31±14 milliseconds; P=0.10). In double-mutation carriers (JLNS patients; n=9), QTc was prolonged compared with single-mutation carriers (560±50 versus 470±35 milliseconds; P=0.001). Mean longitudinal contraction duration was prolonged (475±35 versus 440±45 milliseconds; P=0.02), but not in the circumferential direction (430±45 versus 430±50 milliseconds; P=0.98), compared with single-mutation carriers. Longitudinal mechanical dispersion was more pronounced in JLNS patients compared with single-mutation carriers (54±13 versus 34±14 milliseconds; P=0.002).

Figure 5 demonstrates that transmural mechanical dispersion was prominent in LQT2 patients in the posterior septal, anterior septal, and anterior segments. Transmural mechanical dispersion was not present in asymptomatic LQT2 mutation carriers. In JLNS patients, significant transmural mechanical dispersion was present in the posterior septal, anterior septal, anterior, posterolateral, and posterior segments. In LQT1 single-mutation carriers, transmural mechanical dispersion did not reach significant levels in analysis of symptomatic LQT1 patients separately.

Discussion

This study confirms that LQTS patients have myocardial contraction abnormalities. A novel observation in the present study was that LQTS patients have abnormally prolonged contraction in the LV long axis, which reflects the function of myocardial fibers located predominantly in the subendocar-

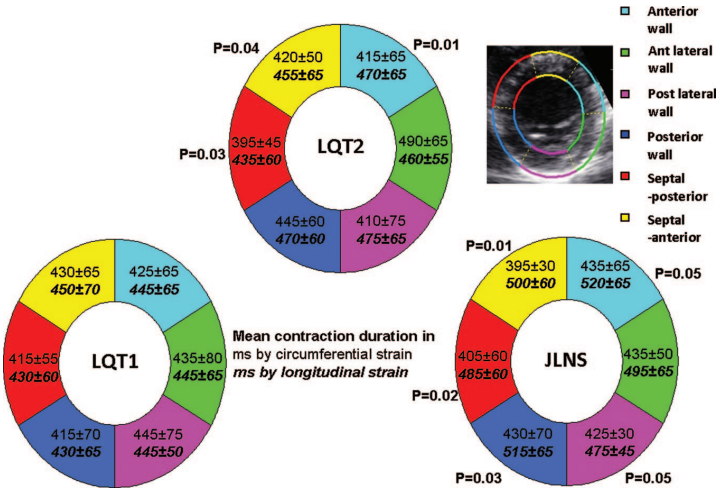

Figure 5. Contraction duration by circumferential and longitudinal strain in 64 LQT1 and 26 LQT2 mutation carriers and in 9 JLNS patients. In LQT2 mutation carriers (top), longitudinal contraction durations (bottom values, italics) in the septal and anterior segments were longer compared with circumferential contraction durations (top values) in the same segments. In JLNS patients (right), longitudinal contraction duration was longer compared with circumferential in all segments except the anterolateral segment. *P* values were obtained by paired *t* test; significant *P* values are presented. Longitudinal contraction durations were significantly longer in JLNS patients compared with LQT1 and LQT2 single-mutation carriers.

dium. The symptomatic LQTS patients in our study had longer contraction duration in the subendocardial layer compared with the mid layer of the ventricular wall, indicating transmural mechanical dispersion. Transmural differences in contraction durations were present in most LV segments, were related to risk for cardiac arrhythmias, and were most evident in LQT2 and JLNS patients. This study indicates that regional myocardial dysfunction may reflect electric disturbances and may be helpful in exploring arrhythmogenesis in these patients.

Electric Dysfunction and Mechanical Consequences in LQTS

Ion channel defects in LQTS lead to prolonged APD. Ion channels are not homogeneously distributed throughout the myocardium. Defective ion channels will therefore lead to an inhomogeneous prolongation of APD and will ultimately result in dispersion of electric repolarization.[2] Findings from LQTS patients have implicated a specific role for early afterdepolarizations and dispersion of electric repolarization in ventricular arrhythmogenesis.[20,21] Furthermore, there is strong evidence that early afterdepolarizations lead to prolonged repolarization, which has been linked to myocardial contraction abnormalities.[8,9]The findings in our study support that prolonged APD results in prolonged regional ventricular contraction and are in accordance with previous studies.[8–10] The pronounced mechanical dispersion found in our LQTS patients was related to ventricular arrhythmias and is likely to reflect electric dispersion. Heterogeneous ventricular contraction can also be caused by fibrosis in myocardial tissue and has been related to ventricular arrhythmias[22] and death[23] in patients after myocardial infarction.

Dispersion of repolarization can occur between the apex and base, ie, longitudinally and transmurally, and can facilitate the generation of torsade de pointes arrhythmia.[21] The measurement of QT dispersion on ECG as an indicator of dispersion of ventricular repolarization was presented as a promising tool in risk stratification of arrhythmias 2 decades ago.[15,16] However, the method has not achieved the clinical value initially expected because of challenges in T-wave definition and relatively low reproducibility.[7] Our study showed pronounced QTc dispersion in LQTS mutation carriers with arrhythmic events compared with those without arrhythmic events (Table 2). This is in accordance with previous studies showing pronounced QT dispersion in LQTS patients with recurrent arrhythmic events.[16] The significant correlation to mechanical dispersion in our study supports the assumption that our echocardiographic findings may reflect electric dispersion of repolarization.

With the method presented in this study, we were able to quantify longitudinal (between the apex and base) and interregional (between the interventricular septum, lateral wall, anterior wall, and posterior wall) mechanical dispersion. In addition, we were able to provide a measure of mechanical transmural dispersion in comparisons of the duration of longitudinal strain with circumferential strain. The fiber orientation in LV is complex. In the subendocardium, the fibers have a predominantly longitudinal direction with an angle of 80° with respect to the circumferential direction.[24,25] A recent experimental study demonstrated that differences in the timing of contraction between circumferential and longitudinal shortening in 1 LV segment were attributed to the electric sequence.[25] The subendocardial fibers contribute mainly to longitudinal contraction, whereas the midmyocardium fibers contribute mainly to circumferential contraction.[13] Therefore, differences in the timing of contraction in these directions reflect the transmural mechanical heterogeneity caused by electric dysfunction.

Mechanical Abnormalities in LQTS Patients

Mean contraction duration was prolonged in LQTS mutation carriers compared with healthy individuals and in symptomatic LQTS mutation carriers compared with asymptomatic carriers. Contraction duration by longitudinal strain (suben-

docardial layers) was significantly longer than by circumferential strain (midmyocardial layers) in symptomatic LQTS patients. These findings indicate a transmural mechanical dispersion in symptomatic LQTS patients that was not present in asymptomatic and healthy individuals. These mechanical findings are in accordance with previous electric LQTS models reporting the longest APD in Purkinje cells and M cells located in the subendocardium and midmyocardium.[4,5,26] The APD of subendocardial Purkinje fibers in vitro has been reported to be even longer than in the M cells, but the delayed repolarization of the Purkinje system has failed to register on the ECG.[5] Purkinje cells are found in the His bundle and bundle branches and cover much of the endocardium.[26] The transmural mechanical dispersion in this study may represent the transmural electric dispersion of repolarization that is shown to be present in LQTS models and is suggested to be a strong arrhythmogenic factor.[21] In symptomatic LQT2 patients, the transmural dispersion was present in the interventricular septum and anterior LV wall. Septal cells may play a specific role in arrhythmogenesis in LQTS.[27] It has been indicated that M cells in the interventricular septum are located in the deep subendocardium and exert a strong electrotonic influence to prolong APD in neighboring endocardial cells.[5] Despite the limited number of genotype subgroup participants, transmural mechanical dispersion was pronounced in LQT2 patients and patients with JLNS. This finding may indicate genotype-specific differences in electric dispersion and are in accordance with the higher arrhythmic risk in patients with these genotypes.[28,29]

Interestingly, our study indicates that novel echocardiographic methods can detect prolonged contraction in the subendocardial layers and support experimental electrophysiological reports. Our findings support the idea of LQTS as a regional disease, with the most prolonged contraction duration in the subendocardium in mutation carriers with arrhythmias. Future studies are needed to explore whether contraction abnormalities can add information about arrhythmogenicity in other channelopathies.

Global strain has been reported as a sensitive marker of systolic function.[17] Global strain was within the normal range in LQTS patients but was reduced compared with healthy individuals. This finding may indicate that the contraction abnormalities in these patients may lead to subclinical impairment of myocardial function.

Electromechanical Interactions in LQTS

Sporadic but consistent awareness that electric alterations in LQTS patients have mechanical consequences has arisen during the past 20 years.[8,9,30,31] We recently reported prolonged myocardial contraction duration and mechanical dispersion by myocardial velocities in LQTS patients that were associated with increased risk for ventricular arrhythmias.[10] However, our recent report and earlier studies were not designed to distinctly quantify separate regions of the myocardium for comparison. In this study, we have used myocardial strain measurements instead of velocity measurements. Myocardial velocities have limited ability to reflect regional myocardial function.[12] In contrast, myocardial strain measurements can identify myocardial dysfunction of a more regional character and can accurately assess myocardial shortening in a distinct part of the ventricle. With this method, we were able to investigate the regional nature of contraction prolongation in LQTS patients.

Time measurements can be performed by speckle tracking and TDI techniques. In our study, contraction duration measured by both techniques showed similar results. The speckle tracking technique has lower temporal resolution than TDI, but it is less ultra-beam-angle dependent and more attractive to use. The preferred technique depends on the investigator's experience.

The specific patterns of myocardial contraction abnormalities described in our study may depend on the concomitant electric disorder in these patients. It is well established that electric alterations are a prerequisite to arrhythmogenic activity. A careful tracing of myocardial strain will thus increase our knowledge of the pathophysiology in LQTS patients and may contribute to risk stratification in clinical routine.

Clinical Implications

Genetic testing for LQTS has become more available; consequently, family screening has led to asymptomatic family mutation carriers making up a great number of consultations at the outpatient clinic. The overall risk that asymptomatic adult mutation-positive family members will experience spontaneous arrhythmias during their lifetime is low, and in these individuals, QTc has failed to be a significant predictor of outcome.[32] Prophylactic treatment involves lifelong β-blocker therapy.[33] Determining whether these family members are true silent mutation carriers and do not need prophylactic medication is often difficult.

By ROC analysis, the best parameter for arrhythmia risk assessment in this study was longitudinal mechanical dispersion. This parameter reflects heterogeneity in regional contraction duration and was superior to QTc in discriminating between LQTS patients with and without arrhythmic events. Our findings suggest that echocardiography might be a complementary tool to QTc in risk stratification of LQTS mutation carriers and may provide added value in risk stratification of asymptomatic adult mutation carriers.

Limitations

The relationship between mechanical dispersion and electric dispersion should be studied in invasive electrophysiological studies. It may be speculated that β-blocker medication might influence contraction duration and our data. However, heart rate was not significantly different in asymptomatic and symptomatic patients, and all time measurements were corrected for heart rate by the Bazett formula. In addition, our recent study comparing healthy individuals on β-blocker medication with LQTS patients could not attribute prolonged contraction duration to the use of β-blocker medication.[10]

Our study did not provide data that demonstrated that LQTS patients with pronounced mechanical dispersion had a higher risk of future arrhythmic events. This requires a

prospective study in which so far asymptomatic and untreated patients are followed up for an adequate period of time. This study design is difficult for ethical reasons.

Conclusions

LQTS patients have regional myocardial dysfunction that can be assessed by myocardial strain. Myocardial contraction duration is prolonged in LQTS mutation carriers and most prolonged in those with arrhythmic events. LQTS mutation carriers with arrhythmic events have longer contraction duration in the subendocardial layer compared with the mid layer of the ventricular wall, indicating transmural mechanical dispersion that is not present in asymptomatic LQTS mutation carriers and healthy individuals. Transmural dispersion is located predominantly in the interventricular septum and anterior LV wall in LQT2 patients and patients with JLNS.

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Disclosures

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CLINICAL PERSPECTIVE

The long-QT syndrome (LQTS) is due to inherited cardiac ion channel defects and predisposes to life-threatening ventricular arrhythmias and sudden cardiac death. Current risk stratification of ventricular arrhythmias is based on a history of syncope or documented arrhythmia, heart rate–corrected QT interval on the ECG (QTc), gender, and genotype. However, QTc is insufficient as a significant predictor of arrhythmic outcome. LQTS has traditionally been regarded as a purely electric disease. Strain by echocardiography can accurately quantify regional myocardial timing and function. Echocardiography was performed in 101 genotyped LQTS patients (53 asymptomatic and 48 with a history of cardiac arrhythmias) and 35 healthy control subjects. Left ventricular contraction pattern by strain was assessed as time from the ECG Q wave to maximum myocardial shortening in 16 LV segments. Strain was assessed along the longitudinal axis, predominantly representing subendocardial fibers, and along the circumferential axis, representing midmyocardial fibers. This study shows that LQTS patients have abnormal LV contraction patterns. Contraction duration was longer and more heterogeneous in symptomatic LQTS mutation carriers compared with asymptomatic patients. In addition, contraction duration was longer in the subendocardium than in the midmyocardium, indicating a pronounced transmural mechanical dispersion that was not present in asymptomatic and healthy individuals. Our findings suggest that echocardiography might be a complementary tool to QTc and may provide added value in risk stratification of LQTS mutation carriers.

III

IV

Right Ventricular Mechanical Dispersion is Related to Malignant Arrhythmias – a Study of Patients With Arrhythmogenic Right Ventricular Cardiomyopathy and Subclinical Right Ventricular Dysfunction

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a chronic, progressive, heritable cardiomyopathy and is one of the leading causes of sudden unexpected cardiac death in previously healthy young individuals [1, 2]. The first clinical symptom may present as life-threatening arrhythmias

ARVC was initially recognized as a disease of the right ventricular (RV) myocardium, but involvement of the left ventricular (LV) myocardium is now commonly recognized [3-6]. Four clinical stages have been documented: An early concealed phase, overt electrical disorder, isolated right heart failure, and biventricular pump failure [2, 4].

Recent molecular genetic reports have revealed ARVC as mainly an autosomal dominant inherited desmosomal disease [7], leading to progressive loss of cardiac myocytes, followed by fibro-fatty replacement. Penetrance is age and gender dependent and the progressive clinical picture is highly variable [8]. Importantly, life-threatening arrhythmias can occur with only discrete or even absent myocardial structural changes [9, 10]. Risk stratification of malignant arrhythmias in so far asymptomatic mutation carriers is therefore challenging.

Echocardiographic studies of the RV in ARVC patients have shown that RV dilatation and reduced regional or global RV function are traits of the disease. Quantitative assessment of RV function is difficult due to complicated anatomy and load dependency. Reviewed guidelines for diagnosing ARVC from 2010 have improved quantitative assessment of RV dysfunction, including measures of RVOT and RV area [11].

Strain by echocardiography has been introduced as an accurate tool for assessment of regional[12] and global myocardial function[13] and recent reports have shown that RV function can be accurately assessed by this method [14].

Electrical conduction delay with consequent electrical dispersion has been suggested as a mechanism of ventricular arrhythmias in ARVC patients [15, 16]. Mechanical dispersion (heterogeneous contraction) assessed by myocardial strain may reflect electrical dispersion and has recently been demonstrated to relate to malignant ventricular arrhythmias in patients with long QT syndrome [17] and in patients after myocardial infarction [18].

We hypothesized that pronounced mechanical dispersion by myocardial strain is associated with susceptibility to ventricular arrhythmia in patients with ARVC and therefore may be an additional tool for arrhythmia risk stratification. Furthermore, we aimed to investigate to what extent LV function assessed by strain echocardiography was reduced along with RV function in patients with ARVC diagnosis and in asymptomatic mutation carriers.

Methods

In total, 59 patients (Table 1) were included. Of these, 36 were diagnosed with ARVC based on the modified International Task Force criteria from 2010 [11], 23 patients were asymptomatic mutation carriers included by family cascade genetic screening (Table 2).

The medication received at the time of the echocardiographic study and the presence of an implanted cardioverter defibrillator (ICD) was recorded.

Healthy control subjects were recruited from the hospital staff. They had normal electrocardiogram (ECG), physical examination, echocardiographic study and were free from disease with potential impact on the cardiovascular system.

Written informed consent was given by all study participants. The study complies with the Declaration of Helsinki and is approved by the Regional Committee for Medical Research Ethics (NEM South).

Genetic analyses

Genomic DNA was isolated from peripheral blood in patients with ARVC phenotype. The individual exons with flanking intron sequences of the genes *plakophilin-2* (*PKP2*), *desmoglein-2* (*DSG-2*) and *desmoplakin* (*DSP*) and 29 of the 105 exons of the *ryanodine receptor-2* (*RYR2*) gene were sequenced by polymerase chain reaction amplification in combination with direct sequencing. Cascade genetic screening was performed in family members of mutation positive ARVC patients.

Two-dimensional (2D) Echocardiography

Patients and control subjects underwent an echocardiographic study (Vivid 7, General Electric, Vingmed, Horten, Norway). Cineloops from 3 standard apical views (4-chamber, 2-chamber and apical long-axis) were recorded using grey-scale harmonic imaging. Data were digitally stored for off-line analysis using software (EchoPac, General Electric, Vingmed, Horten, Norway). The echocardiographic data were analyzed blinded to all clinical information including presence of arrhythmia in ARVC patients.

From 2D echocardiography the following parameters were assessed: Right ventricular outflow tract (RVOT) diameter in the parasternal short axis view, right ventricular end-diastolic (RVED) area, right ventricular end-systolic (RVES) area and right ventricular area fraction (RVAF) from apical 4 chamber view[11].

2D Strain and Dispersion

The endocardial borders were traced in the end-systolic frame of the 2D images from the 3 apical views for LV strain and from the 4-chamber view for RV strain. Speckles were tracked frame-by-frame throughout the LV and RV wall during the cardiac cycle. Segments that failed to track, were manually adjusted by the operator. Any segments that subsequently failed to track, were excluded. Peak systolic myocardial strain by 2D speckle tracking echocardiography was

assessed in 16 LV segments and averaged to LV global longitudinal strain. Peak systolic strain from 3 RV free wall segments was averaged as a measure of RV function (RV strain). Contraction duration (CD) (Figure 1) was measured as time from onset R on ECG to maximum LV and RV shortening by strain. Standard deviation (SD) of CD was calculated as a parameter of mechanical dispersion, in a 16 LV segment and a 6 RV segment model.

We used a 6 RV segment model (3 RV free wall segments plus 3 septal segments) when assessing mechanical dispersion which includes the usually less affected interventricular septum[11] to elucidate dispersion of contraction between affected and non-affected segments.

Magnetic Resonance Imaging (MRI)

MRI was performed using 1.5 Tesla units (Magnetom Vision Plus or Magnetom Sonata, Siemens, Erlangen, Germany) and a phased array body coil. Axial and sagital T1 TSE images, multiple axial and one sagital cineloop covering the RV and LV were recorded. RV and LV chamber dimensions, wall thickness, fatty infiltration and myocardial function were assessed.

Signal-Averaged ECG (SAECG)

SAECG was performed using a MAC® 5000-analysing system (GE Medical Systems, Milwaukee, Wisconsin, USA). Time domain analysis was obtained in the bandpass filter 40 to 250 Hz. The SAECG was considered positive for late potentials when at least two of the following parameters were abnormal: total filtered QRS duration (fQRSd) >114 ms, the terminal (last 40ms) QRS root mean square voltage (RMS) <20μV and the low amplitude (<40μV) late potential duration (HFLA) >38 ms.

Statistical analyses

Analyses were carried out using a standard statistical software program (SPSS version 16, SPSS Inc, Chicago, Ill). Data were presented as mean ± SD and numbers and percentages, respectively. The chi-square test was used to determine differences between 2 groups of

categorical variables. Student-t test was used to compare differences between 2 groups for continuous variables. Comparisons of means were performed by analysis of variance (ANOVA) with the Bonferroni *post hoc* correction for multiple comparisons. Correlation between RV and LV strain was assessed by linear regression analysis. The value closest to the upper left corner of the receiver-operator characteristic curve determined optimal sensitivity and specificity for the ability of RV mechanical dispersion to identify arrhythmic events. P-values were two-tailed, values below 0.05 were considered significant.

Results

Among 59 patients in this study, 36 (61%) had symptomatic ARVC, while 23 (39%) were asymptomatic mutation carriers, diagnosed by cascade genetic screening. ARVC related mutations were confirmed in 43 (73%) of all patients, [37 (86%) *PKP2*, 5 (12%) *DSP* and 1 (2%) *RYR2*]. No mutations were found in 16 (44%) ARVC patients.

Ventricular arrhythmias (Ventricular Tachycardia (VT) or Ventricular Fibrillation (VF)) were documented in all 36 ARVC patients and 78% of the ARVC patients received anti arrhythmic medical therapy at the time of the echocardiographic study. An ICD was implanted in 33 (92%) of the ARVC patients.

Complete right bundle branch block (RBBB) was present in 3 (9%) and incomplete right bundle branch block in 4 (12%) ARVC patients.

MRI studies were completed in 16 (70%) asymptomatic mutation carriers and in 25 (70%) ARVC patients. Negative MRI study regarding ARVC phenotype was found in 8 (50%) asymptomatic mutation carriers and in 4 (16%) ARVC patients.

Pathological SAECG was significantly more frequent in ARVC patients compared to asymptomatic mutation carriers (p=0.03) (Table 3). QRS duration assessed by ECG and total

filtered QRS duration (fQRSd) assessed by SAECG were prolonged in ARVC patients compared to asymptomatic mutation carriers (0.03 and 0.05, respectively) (Table 3).

Mechanical dispersion in ARVC patients

ARVC patients with arrhythmias showed a marked increase in RV and LV mechanical dispersion compared to asymptomatic mutation carriers ($p<0.01$ and $p<0.001$) and healthy controls (both $p<0.001$) (Table 4). Importantly, asymptomatic mutation carriers showed significantly increased RV and LV mechanical dispersion compared to healthy controls ($p<0.01$ and $p<0.001$), indicating subclinical myocardial alterations. A receiver operator characteristic (ROC) analysis demonstrated that RV mechanical dispersion greater than 42 ms identified arrhythmic events in ARVC patients with a sensitivity of 81% and a specificity of 65% (Figure 2).

Table 5 shows 4 patients (2 presented with VF and 2 with VT) with normal conventional echocardiographic and MRI findings. Despite normal conventional imaging, all 4 had significant increase in mechanical dispersion in RV (48±11ms) and LV (52±11ms) compared to healthy individuals (both $p<0.001$). Three of them had an ARVC related mutation and 1 patient progressed subsequently to typical ARVC phenotype.

RV and LV function

ARVC patients with arrhythmias showed significantly reduced RV and LV function assessed by myocardial strain compared to asymptomatic mutation carriers ($p<0.01$ and $p<0.001$) and healthy controls (both $p<0.001$). LV ejection fraction (EF) was within normal range in ARVC patients with arrhythmias, but was significantly reduced compared to healthy individuals ($p<0.01$) (Table 4).

LV and RV functions by strain were significantly correlated in symptomatic ARVC patients ($R=0.84$, $p<0.001$) (Figure 1). Importantly, this relationship was present in symptomatic

ARVC patients with reduced RV function by visual assessment, indicating biventricular disease in patients with "classic" right ventricular involvement. Reduced LV strain (> -20%) was found in 27 of 36 (75%) patients and 27 (75%) patients had reduced RV strain (> -25%). Reduced myocardial function in both ventricles was present in 23 (64%) patients. Four (11%) patients had reduced LV strain along with normal RV strain and 4 (11%) patients had reduced RV strain with normal LV strain. Normal myocardial function in both ventricles was only present in 3 patients (8%).

Asymptomatic mutation carriers had LV strain within normal range (-20 ± 2 %), but importantly, RV and LV function assessed by strain were significantly reduced compared to healthy individuals ($p<0.05$), indicating subclinical myocardial impairment (Table 4).

ARVC patients with arrhythmias had significantly increased RVOT diameter, RVED area and RVES area ($p<0.001$, $p=0.01$ and $p=0.003$) and significantly reduced RVAF ($p=0.001$) compared to asymptomatic mutation carriers (Table 4).

Discussion

This study demonstrates that mechanical dispersion assessed by speckle tracking echocardiography is closely related to ventricular arrhythmias in patients with ARVC. Increased mechanical dispersion and reduced myocardial strain in both ventricles were present in asymptomatic mutation carriers, indicating subclinical myocardial alterations. Importantly, pronounced mechanical dispersion was also present in individuals who had experienced arrhythmias in the early stages of ARVC when structural alterations assessed by conventional echocardiography and MRI were absent. These findings indicate that mechanical dispersion may be evaluated as a marker of arrhythmias in so far asymptomatic mutation carriers and may be helpful in risk stratification.

The relationship between mechanical dispersion and arrhythmias

The diagnosis of ARVC is challenging and the prediction of which patients will develop arrhythmias is even more so. No single test is sufficient to diagnose or exclude ARVC and to predict arrhythmias. The Task Force criteria from 1994 [19] are highly specific but lack sensitivity for early stages and familial forms of ARVC. Overall sensitivity have been enhanced by the 2010 revision [11]. However, risk assessment of malignant arrhythmias in the early stages remains a challenge.

The occurrence of malignant arrhythmias in the early stages can precede structural myocardial changes shown by traditional imaging techniques. An accurate assessment of myocardial function is therefore particularly important in early ARVC, e.g. in so far asymptomatic mutation carriers. Myocardial strain by echocardiography has demonstrated to be a sensitive tool for assessing ventricular function and timing [20].

In our study, we demonstrate that evaluation of regional timing in terms of mechanical dispersion may add important diagnostic and prognostic information in ARVC, particularly in the early stages of the disease. We demonstrate a significant increase in mechanical dispersion in both ventricles in asymptomatic mutation carriers who apparently have structurally and functionally normal LV and RV by traditional echocardiography and MRI. More importantly, these findings may be used for risk prediction of life-threatening arrhythmias in asymptomatic mutation carriers.

Interestingly, reduced myocardial strain and increased mechanical dispersion in both ventricles showed significant differences between healthy controls and asymptomatic mutation carriers. These findings suggest biventricular involvement also in the concealed phase of the

disease when structural and functional changes are not apparent if assessed by traditional echocardiography or MRI.

We have recently demonstrated mechanical dispersion to be related to ventricular arrhythmias in patients with long QT syndrome [17]. Furthermore, we have introduced mechanical dispersion as a predictor of ventricular arrhythmias in patients after myocardial infarction [18]. The present study shows that mechanical dispersion is present in ARVC patients, and may help to risk stratify arrhythmic events. The mechanisms of arrhythmogenesis in infracted tissue and in ARVC have similarities in terms of fibrosis and delayed electrical conduction. Altered electrical conduction is present in ARVC in the phase of overt electrical disorder, while fibrosis may develop later [9, 10]. Dispersion of ventricular depolarization-repolarization has been regarded as a strong arrhythmogenic factor, although non-invasive assessment of these electrical abnormalities have been challenging [16]. Electrical abnormalities in diseased myocardium may be translated into mechanical alterations. Mechanical dispersion by strain echocardiography appears to be a sensitive tool for assessing subtle changes in timing of myocardial contraction.

Ventricular arrhythmias in ARVC are believed to origin from different mechanisms at different stages of the disease. In the concealed phase, inflammatory processes due to apoptosis, derangements in cell-to-cell adhesion and altered nuclear signaling are reported to be arrhythmogenic [9, 10]. A study using immunohistochemistry has shown reduced levels of gap junction protein Connexin 43, important for myocardial electrical propagation, in a patient homozygous for ARVC mutations, but without visible structural alterations [10]. Our study may support these findings, indicating subtle contraction heterogeneity in asymptomatic mutation carriers. In later stages of the disease, islands of surviving myocytes surrounded by fibro-fatty tissue provide a substrate for re-entry ventricular arrhythmias [2, 16]. The novelty of the present study is the identification of myocardial abnormalities in the early stages, and the potential for

prediction of arrhythmias. However, these findings have to be confirmed in a prospective and longitudinal study.

RV and LV dysfunction or biventricular disease

Initially, ARVC was believed to be a pure RV disease. New subtypes of arrhythmogenic cardiomyopathy with LV or biventricular predilection have been recognized [4]. Importantly, progression from left-dominant to biventricular involvement has also been documented [21].

LV involvement was first suggested in 1983 [3] and has been confirmed in several studies [6, 21, 22]. A recent study using echocardiographic tissue Doppler imaging (TDI) showed signs of LV involvement in patients with only mildly decreased RV function[23],. Our study showed similar results. Decreased myocardial strain and increased mechanical dispersion in both ventricles in asymptomatic mutation carriers and in symptomatic ARVC patients diagnosed by current guidelines [11], suggest early involvement of the LV. Furthermore, LV and RV strain were significantly correlated in our ARVC patients. Biventricular impairment is probably a result of biventricular ARVC affection, but mutual dependency of RV and LV hemodynamics may be considered.

Current diagnostic tools

The diagnosis of ARVC is based on the criteria outlined by the International Task Force [19] in 1994, and revised in 2010 [11]. Criteria for structural abnormalities are based on 2D echocardiographic and MRI findings. Since the establishment of these criteria, several studies have confirmed the ability of MRI to detect structural abnormalities and myocardial fatty replacement in patients with ARVC [24, 25]. Despite, the excellent abilities of MRI to diagnose ARVC, our study demonstrates that novel echocardiographic methods were able to detect ventricular abnormalities in patients with normal MRI findings. Novel echocardiographic methods such as TDI and strain echocardiography are at present not widely used in the diagnostic

and prognostic work-up of patients with ARVC. However, since echocardiography is easily available, it might be a promising tool for detecting RV and LV abnormalities in patients with ARVC.

The most significant development of ARVC research the latest years is the identification of mutations in genes encoding desmosomal and extradesmosomal proteins [2]. Pathogenic mutations in the gene encoding the desmosomal protein *PKP2* are particularly prevalent and have been identified in up to 43% of cases [4, 26, 27]. Since the disease is inherited in up to 50% of cases, the screening of relatives is important.

Clinical implications

Recognizing ARVC as a familial disease has resulted in screening of family members. In mutation positive ARVC patients, cascade genetic screening helps focusing resources on affected family members. Still, risk stratification in these asymptomatic mutation positive family members is challenging and emphasized by the fact that the first manifestation of the disease in 20-50% of cases may be cardiac arrest [28]. Guidelines for treatment of asymptomatic mutation carriers are sparse [27]. The novel methods presented in this study demonstrated subclinical myocardial impairments which were associated with risk of ventricular arrhythmias. These methods may therefore be of help in risk stratification of so far asymptomatic mutation carriers.

Study limitations

The echocardiographic data were analyzed blinded to all clinical information. However, ICD leads are visible on echocardiography, thus demasking the disease status of the patients.

We assessed global longitudinal strain but not radial or circumferential strain. This measure was chosen because longitudinal strain has been best validated. Measurements are reproducible and are easily obtained with only a minor increase of procedure duration. Radial and circumferential strains from the RV are more difficult to obtain due to the complicated anatomy.

Conclusions

This study demonstrates that mechanical dispersion assessed by speckle tracking echocardiography is closely related to ventricular arrhythmias in patients with ARVC. Mechanical dispersion was present in asymptomatic mutation carriers, indicating subclinical myocardial involvement. Likewise, pronounced mechanical dispersion was present in ARVC patients who had experienced ventricular arrhythmias in the early stages of the disease. These findings indicate that mechanical dispersion may serve as a risk stratification tool in asymptomatic mutation carriers, and be helpful in decisions regarding prophylactic treatment.

RV and LV function correlated in ARVC patients and asymptomatic mutation carriers, which implies that ARVC is a biventricular disease. LV involvement was present at the early stages of the disease, and echocardiographic evaluation by strain measurements appears to be a sensitive marker of subclinical LV involvement.

Conflict of Interest: none declared

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Figure Legends

Figure 1. Mechanical dispersion in an asymptomatic mutation carrier (left panel) and an ARVC patient with recurrent arrhythmias (right panel).
Horizontal white arrow indicates contraction duration defined as the time from onset R to maximum myocardial shortening. Vertical arrows indicate the timing of maximum myocardial shortening in each segment. Right panel shows more pronounced mechanical dispersion.

Figure 2. RV versus LV strain in 36 ARVC patients with arrhythmias. The correlation between RV and LV function was $R = 0.84$, $p<0.001$.

Figure 3. Receiver-operator characteristic curve for RV mechanical dispersion. RV mechanical dispersion more than 42 ms could identify cardiac arrhythmic events with a sensitivity of 81% and a specificity of 65%. Area under curve 0.76 (95% CI 0.75-0.92).

Table 1 Clinical characteristics

	Healthy individuals (n=30)	Asymptomatic mutation carriers (n=23)	ARVC patients with arrhythmia (n=36)	p-value
Age (years)	41.0±15.6	38.3±19.7	44.2±15.5	0.40
Male n(%)	16(53%)	13(57%)	21(58%)	0.98
Heart rate (bpm)	66±11	66±13	60±14	0.13

Mean±SD, Numbers (percentages). Right column shows *P*-values for ANOVA and chi-square tests.

ANOVA, analysis of variance

Table 2. Findings according to current International Task Force criteria (2010)

		Asymptomatic mutation carriers (n=23)	ARVC patients with arrhythmia (n=36)	p-value
Positive family history n(%)	**Major**	21(91%)	22(61%)	0.01
	Minor	20(87%)	11(31%)	<0.001
ECG depolarization/ conduction abnormalities n(%)	**Major**	0	8(23%)	0.01
	Minor	5(25%)	15(56%)	0.04
Repolarization Abnormalities n(%)	**Minor**	3(13%)	20(57%)	0.001
Tissue characterization of walls n(%)	**Major**	N/A	N/A	N/A
Global and/or regional dysfunction and structural alterations by echocardiography/MRI n(%)	**Major**	2(9%)	18(50%)	0.001
	Minor	6(27%)	13(36%)	0.49
Arrhythmias n(%)	**Minor**	0	36(100%)	<0.001

Mean±SD, Numbers (percentages). Right column shows *P*-values for ANOVA and chi-square tests.

ANOVA, analysis of variance; N/A=Not Applicable

Table 3. ECG and SAECG findings

	Asymptomatic mutation carriers (n=23)	ARVC patients with arrhythmia (n=36)	p-value
QRS(ms)	93±12	104±23	0.03
QTc(ms)	424±26	440±37	0.07
SAECG fQRSd(ms)	109±28	126±27	0.05
SAECG HFLA(ms)	38±14	47±29	0.20
SAECG RMS(μV)	33±19	26±22	0.25
SAECG positive(n)	5(25%)	16(57%)	0.03

Mean±SD, Numbers (percentages). Right column shows *P*-values for ANOVA and chi-square tests.

ANOVA, analysis of variance; fQRSd, filtered QRS duration; HFLA,Low amplitude (<40μV) late potential duration; QTc, QT interval corrected for heart rate; RMS, terminal (last 40ms) QRS root mean square voltage

Table 4. Echocardiographic results

	Healthy individuals (n=30)	Asymptomatic mutation carriers (n=23)	ARVC patients with arrhythmia (n=36)	p-value
EF(%)	64±5	63±4	57±14*	<0.01
LV GLS(%)	-23±2	-20±2*	-16±5*·**	<0.001
RV strain(%)	-28±5	-24±5*	-19±7*·**	<0.001
LV Dispersion(ms)	22±8	42±13*	64±25*·**	<0.001
RV Dispersion(ms)	15±8	33±20*	53±25*·**	<0.001
PSAX RVOT(mm)		28±3	33±4	<0.001
RVED area(cm²)		25±6	30±7	0.01
RVES area(cm²)		15±5	20±7	0.003
RVAF(%)		44±7	35±10	0.001

Mean±SD. Right column shows *P*-values for ANOVA test. Flags for significance are obtained from the *post hoc* pair-wise comparison using the Bonferroni correction.

*p<0.05 compared with healthy individuals.

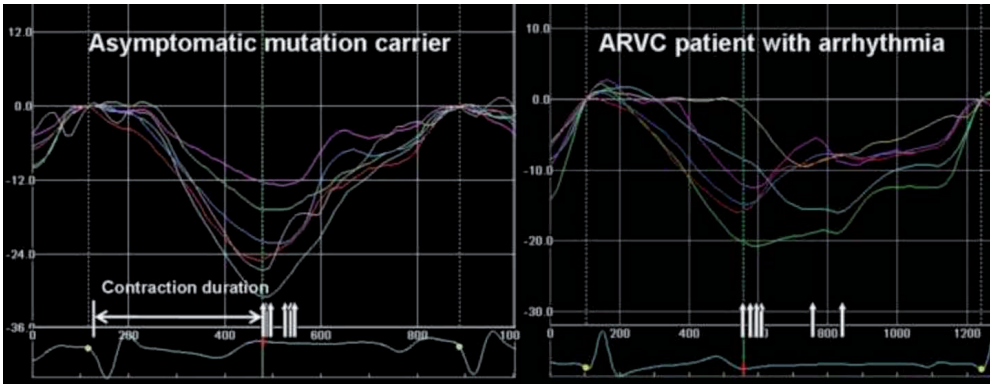
**p<0.01 compared with asymptomatic mutation carriers.

ANOVA, analysis of variance; EF, ejection fraction; GLS, global longitudinal strain; PLAX, parasternal short axis; RVAF, right ventricular area fraction; RVED, right ventricular end-diastolic; RVES, right ventricular end-systolic; RVOT, right ventricular outflow tract

Table 5. Patients with normal echocardiographic and MRI studies at the time of presentation with life threatening arrhythmia

	32 year old female	34 year old male	58 year old male	38 year old male
LVEF(%)	60	64	75	57
LVGLS(%)	-19	-16	-21	-18
RVstrain(%)	-21	-20	-19	-27
LV Dispersion(ms)	41	45	57	65
RV Dispersion(ms)	52	33	58	52
SAECG	neg	pos	pos	pos
Mutation	pos	pos	neg	pos
Arrhythmia	VF	VT	VT	VF

EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle; SAECG, signal-averaged ECG; VF, ventricular fibrillation; VT, ventricular tachycardia



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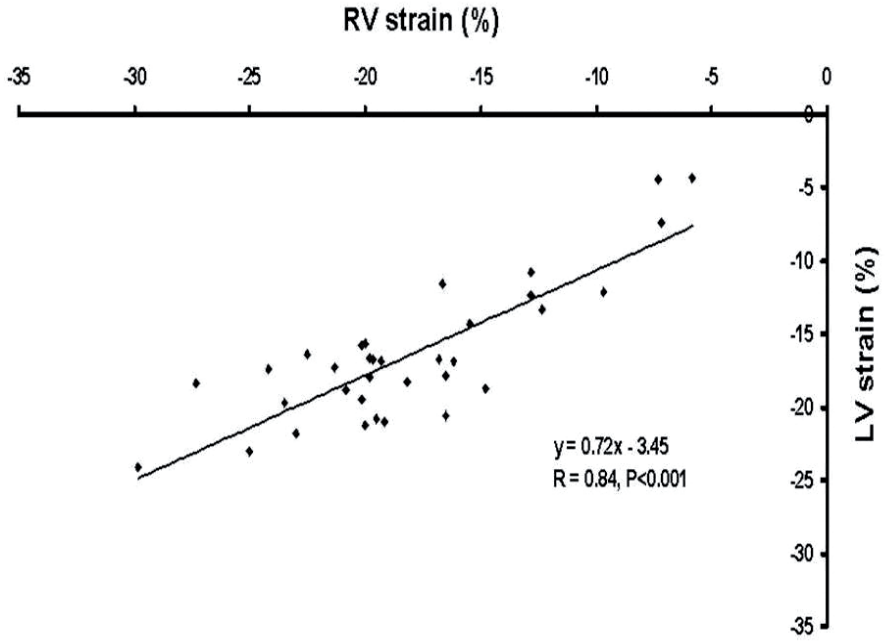

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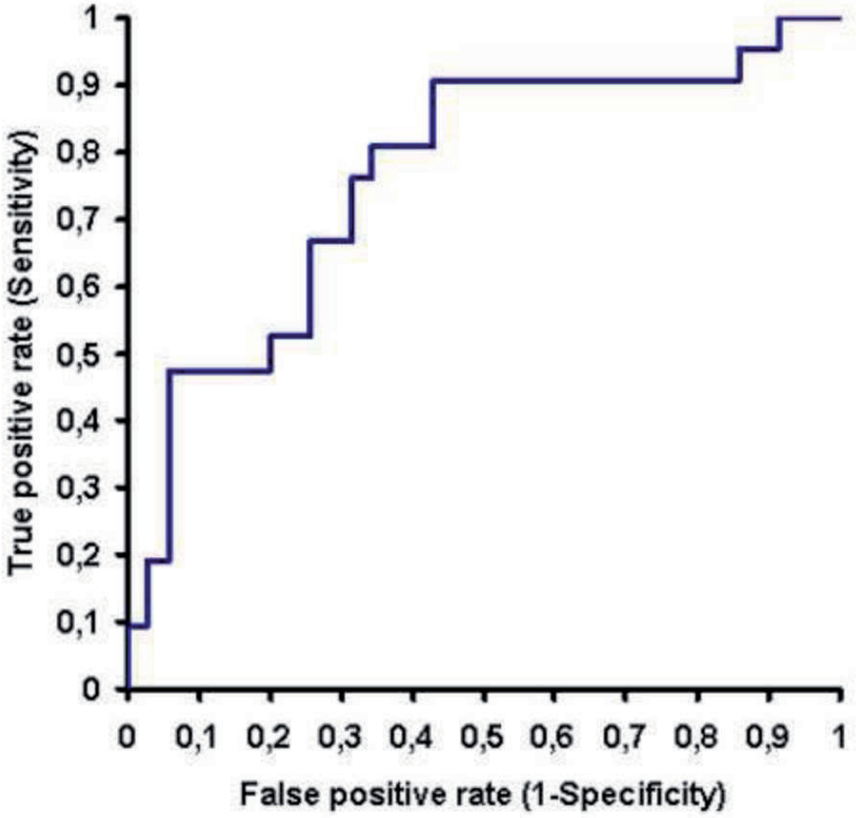

Figure 3. Receiver-operator characteristic curve for RV mechanical dispersion. RV mechanical dispersion more than 42 ms could identify cardiac arrhythmic events with a sensitivity of 81% and a specificity of 65%. Area under curve 0.76 (95% CI 0.75-0.92).